ANALYSIS OF PROGRAM ACTIVITIES
NATIONAL INSTITUTES OF HEALTH
1954

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

NATIONAL INSTITUTES OF HEALTH
PUBLIC HEALTH SERVICE
U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

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Analysis of NIH Program Activities

January-December 1954

U.S National Institute of Arthritis and Metabolic Diseases
Laboratory Research

The laboratory research activities in NIAMD encompass both basic and applied studies. The following highlights of research progress in 1954 make no distinction between these types of studies since there is no real line which divides the two. Basic studies are generally classified as such only because our knowledge is not sufficiently advanced to foresee their implications and applications.

Amino Acids are not only the basic building blocks for proteins but enter into metabolic reactions in many ways. Derangements in amino acid metabolism are found in human diseases such as cystinuria, phenylpyruvic oligophrenia and alkaptonuria. During the past year NIAMD scientists have contributed to our knowledge of amino acid metabolism on several fronts. Aspartic acid has been shown, for the first time, to be a precursor of asparagine and of homoserine. Histidinal has been shown to be a precursor for the biosynthesis of histidine. Two new enzyme reactions involving imidazole acetal phosphate were shown to be involved in the biosynthesis of histidine. One of these represents a new type of transamination reaction. A previously unknown enzyme has been found which is involved in the conversion of the amino acid tryptophan to the vitamin niacin. 5 and 7-hydroxytryptophan, -tryptamine and -(hetero) auxin were synthesized and some of the compounds identified with new metabolites of tryptophan. A chemical method has been developed to convert histidine via the new (allo)-hydroxyornithines to (allo) hydroxyproline (of interest as a constituent of connective tissue).

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Animals with diabetes have been found to be unable to convert tryptophan to niacin - a defect correctable by insulin. Methionine appears to diminish animals (chicks) requirement for vitamin B_{12}.

Amines - These substances are closely related to amino acids and are involved in many physiologic and toxicologic problems in health and disease. Histamine is a powerful substance which appears to be important in gastric secretion, in certain types of neural transmission, in allergy and anaphylaxis and in stimulating the pituitary-adrenal system. NIAMD scientists have studied systematically the biosynthesis and breakdown of this important amine. During the past year imidazoleacetic acid riboside was identified as a major intermediate in the metabolism of histamine. Spermine and related amines have been investigated since they are potent kidney damaging agents. Spermidine, putresine and an amino aldehyde have been identified as the breakdown products of spermine. An enzyme has been found which protects animals against lethal doses of spermine.

Proteins are not only a major structural element of all tissue but function in many ways as enzymes, hormones, immune antibodies, in blood coagulation and muscle contraction, in maintaining normal osmotic pressure, and as carriers of important substances. The processes by which proteins are arranged in an orderl fashion to form biological structures are being studied, for example, in muscle contraction and in blood coagulation. Two peptide fragments have been identified which appear during blood coagulation. ATP splitting and contraction of muscle fibers are not correlated as once thought. In addition to ATP and ITP, it has been shown that the inorganic salts KSCN and KI can cause muscle fibers and myosin threads to contract. Both human and bovine serum albumin were induced to polymerize reversibly under the influence of hydrogen ions and salts. The amino acid

lysine has been discovered in the protein salmine. Salmine is not a homogenous protein as previously believed. A peptide was found in human gamma globulin preparations which inhibits the agglutinin reaction characteristic of rheumatoid arthritis.

Carbohydrates are a major dietary and metabolic fuel and provide building blocks for the synthesis of many important metabolites and structural elements in tissues. An intimate understanding of carbohydrate metabolism is basic to improved methods of preventing and treating diabetes and many other diseases. Much attention has been given to a relatively unexplored "alternate" pathway of carbohydrate metabolism. NIAMD scientists found that in liver about 44% of glucose is catabolized via the conventional glycolytic pathway whereas about 56% appeared to be oxidized presumably via the "alternate" oxidative route. Liver from rats which were diabetic or fasted appeared to use the glycolytic pathway to a greater extent. Muscle from diaphragm appeared to use the glycolytic mechanism exclusively.

Important further progress has been made in elucidating the detailed mechanisms of the "alternate" pathway. D-xylulose phosphate, D-erythrose 4-phosphate and sedoheptulose diphosphate have been definitely identified for the first time as being involved in this scheme of carbohydrate metabolism. Another new metabolite, erythro-3-ketopentose phosphate, has been identified tentatively.

Glycogen is a complex sugar which constitutes a major storehouse of quickly available energy. Although glycogen yields only glucose on total hydrolysis, it is metabolically inhomogeneous. Glucose residues are added to or removed from the periphery of the molecule quite readily, but find their way into the central portions of the molecule more slowly by a continual process of branching.

Basic to the above investigations are the studies in the chemistry of carbohydrates which NIAMD has conducted for many years. Six new crystalline heptoses, heptuloses and hepitols, and ribose orthoester derivatives of unique structure were prepared and characterized; the structure of the carbohydrate moities in stevioside, a non-toxic substance of plant origin which is 300 times as sweet as sugar, was determined. Hitherto unknown types of linkages were found in this molecule.

Vitamins - Substantial progress has been made in purifying Factor 3 which protects against acute necrotic liver degeneration in animals. Concentrates of 26,000 fold purification can now be produced. An 18 hour *in vitro* test for Factor 3 has been developed. The immediate cause of death of animals with this disease has been found to be hypoglycemia and fascular shock. A metabolic respiration defect in their livers (histologically normal) can be reversed in acut experiments with vitamin E or Factor 3. The earliest reco nizable pathological finding in these livers is in the mitochondria.

Tentative evidence has been obtained for one or more unidentified growth factors in the chick. The amount of dietary fat has been shown to cause a 20 fold difference in the vitamin B_{12} requirement of chicks. The urinary compound excreted by folic acid deficient rats has been identified as formimino glutamic acid. N^{10}-formyl folic acid has been isolated and identified from liver. A labile reduced form of this compound may be present in human urine following folic acid administration. Large amounts of vitamin C decrease dietary requirements for riboflavin and pantothenic acid in dogs as previously shown for rats. Treatment of diets with ethylene oxide (sometimes used commercially) caused marked nutritional deterioration due in part at least to destruction of thiamine,

riboflavin and to a lesser extent folic acid and niacin. Choline deficiency and fat deficiency have been produced in guinea pigs for the first time and the deficiency states characterized. Choline deficiency in the guinea pig differed from that in other species since no marked fatty livers were observed; no kidney herorrhages were found but small hemorahages in the adrenal and subcutaneous tissue were noted.

Fat - Obesity has been induced in rats by high fat diets. These animals have been shown to have a very low tolerance to high altitude hypoxia. Pathologic studies showed degeneration of the B cells of the anterior pituitary and osteoarthritis. The kidneys were 2 to 3 times normal size with hemorrhagic areas and pitted cortices. Testes and seminal vesicles were small and degenerated. Livers were enlarged and fatty in many instances. Obesity was also induced in mice by transplanting ACTH producing tumors. Using fertile frog eggs in which the fat and protein was tagged with C^{14}, it was found that C^{14} activity in fat dropped as development progressed, unless carbohydrate was supplied. Drugs such as dinitrophenol altered this pattern and produced changes in protein as well. Some evidence was obtained that guinea pigs may have a dietary requirement for fat *per se* in addition to needing essential fatty acids.

Minerals - The mechanisms by which the body compartmentalizes various inorganic ions and fluid to maintain a relatively constant yet different environment inside and outside of cells, but permits passage of these substances when needed, is a fundamental characteristic of living cells. NIAMD scientists using *in vitro* model systems have discovered a mechanism which explains the accumulation of ions against a concentration gradient and have developed a theory to account for the differential accumulation of, for example, potassium over sodium across

a membrane. The entry and exit of sodium, potassium and chloride in nerves has been studied in relation to nerve function under conditions of oxygen lack and in the presence of certain drugs. Previously unsuspected interrelations between sodium, potassium and calcium have been found in nutrition studies in rabbits. Extremely small amounts of copper have been found to be required for the conversion of pentose phosphate to a new pentose tentatively identified as erythro-3-ketopentose.

Hormones - Several advances have been made in this field which are so vital to the research mission of NIAMD. A reliable method has been developed to assay thyrotrophic hormone and methods to assay adrenal hormones in body fluids have been developed. Hyperadrenal corticism has been produced in mice by transplanting ACTH producing tumors. Thyroxin has been shown to exert a major effect on protein formation. A meta isomer of thyroxin has been synthesized for testing as a possible antagonist to thyroxin. A method has been developed to study the action of insulin and anti-insulin substances in vitro.

A number of naturally occurring steroidal substances which might be possible precursors for the synthesis of cortisone have been isolated, studied chemically and their structure determined. Chemical rearrangements which might be involved in the conversion of steroids to other substances have been investigated and clarified. In other studies, methods have been developed to study the action of radiant energy on steroids and to isolate and identify the products of the reaction.

Glucuronic acid is of special interest since many toxic compounds, certain medicinals and hormones are excreted from the body in combination with this substance and it is an important constituent of connective tissue. A puzzle of long

standing is that glucuronic acid administered exogenously does not participate in these functions whereas that manufactured in the body does. The validity of this fact in man was confirmed by NIAMD investigators using isotope tracer techniques. This puzzle seems about solved since the mechanism by which glucuronic acid arises in the body is such that glucuronic acid is produced in an "activated" form. A new enzyme, uridinediphosphoglucose dehydrogenase, was found which catalyzed the oxidation of uridinediphosphoglucose to uridinediphosphoglucuronic acid. The latter can serve to donate "active" glucuronic acid for conjugation and detoxification reactions. Other studies have shown that about 1/5 of the adrenal steroids in plasma are present as glucuronides. Progress has been made in chemically synthesizing glucuronides of various steroids for use in research.

Enzymes and Coenzymes - Uridine nucleotides, referred to above, are a relatively new class of metabolic substances, which may have great significance. Uridine pyrophosphate N-acetylglucosamine and uridine pyrophosphate N-acetyl galactosamine sulfate were isolated from natural sources and may be key substances in the synthesis of glycoproteins and mucopolysaccharides which are of basic importance in relation to connective tissues and arthritis. In addition, evidence was obtained that uridine triphosphate may be involved in the contraction of muscle.

A technic has been developed whereby the important enzyme hyalouronidase can be localized and studied histologically in tissues using an antigen-antibody fluorescent dye procedure.

Two new enzymes have been reported which catalyze a new series of transphosphorylation reactions. A new deaminase has been obtained which rapidly converts adenosine to inosine. Two additional enzymes have been discovered which

made possible the identification of 4-aminoimidazole and formimino-glycine as intermediates in the degradation of xanthine and the isolation of a nucleotide not identical with any known compound. An enzyme has been prepared from cell free extracts which catalyzes the conversion of gluconic acid to gluconic acid-6-phosphate.

Nucleic acids are complex materials consisting of nitrogenous bases, phosphates and a pentose sugar. They occur in all cells and are thought to provide the chemical basis of heredity. Important new information in this field has been secured by NIAMD scientists. Enzymes have been found which are capable of synthesizing portions of these complex molecules. Exchange reactions have been discovered which could convert one nucleic acid into another. There are probably hundreds of different nucleic acids each with its own special function. These studies have also clarified many details as to the precise chemical structure of these substances. A new series of transphosphorylation reactions has been discovered which makes possible the synthesis of all the triphosphates which are believed to be precursors in nucleic acid synthesis.

Metabolic studies have shown that midbrain transection is followed by a decreased glucose tolerance, sodium retention, potassium loss, marked creatinuria and in some instances negative nitrogen balance. Creatinine excretion decreased. Transection of the spinal cord (between C.6 and T.3) was followed by similar changes. In other studies utilizing N^{15} labeled glycine, it was shown that patients with muscular dystrophy synthesized creatine at a normal rate but failed to to introduce it into muscle cells at normal rate.

Magnesium sulfate and glutathione had a mutually potentiating effect in protecting against the reproduction inhibiting effect of ratiation in hydra.

Radiation was shown to have a greater effect in preventing the initiation of development (in hydra) than it did in interfering with morphogenesis once development had started.

Photosynthesis, the utilization of radiant energy to produce organic compounds, is the ultimate source of all food. Its chemical and biochemical mechanisms are incompletely understood. NIAMD investigators have studied several enzyme systems in which CO_2 can be incorporated into organic substances. For example, ribulose diphosphate can accept CO_2 to yield two moles of phosphoglyceric acid. In other studies, unicellular organisms such as Chlorella are studied under carefully controlled conditions. Recent findings indicate that pigment density and the relative proportion of pigment components are critical factors in the quantum efficiency of photosynthesis. Cell size, pigment distribution and localization of storage products in the cells also influence photosynthetic efficiency.

Blood - The anemia of platelet deficient dogs was found to be aggravated by the escape of red cells from small vessels. These red cells were absorbed by the lymphatics and returned to the circulation with a shortened life span, presumably due to damage in their extravascular cycle. This finding may be of significance in other forms of thrombocytopenia. While measuring red cell survival with radiochromium, it was found that a changing chromium elution loss was a sensitive indicator of red cell damage. The longevity of turtle erythrocytes was found to be many times longer than in any other animal thus far reported.

Respiration - The acquisition of oxygen and the discharge of CO_2 are fundamental requirements for life in the animal kingdom. The physical factors which govern the passage of respiratory gases through biological structures are

being examined in both fundamental and applied studies. In insects, it was found that a process called "pore diffusion", hitherto described only in plants, was responsible for a large portion of their oxygen uptake. Other insects were found capable of impounding their respiratory CO_2 for long periods, only to release it in great gushes. The mechanism for this was found. Further progress was made in understanding the physiologic and pathologic (especially heart damage) effects of high altitude hypoxia. A type of osteoarthritis was found also in these rats. Hypoxia did not serve as a stimulus to erythropoesis in cold blooded animals such as turtles, nor could this species make the circulatory and respiratory adjustments which warm blooded animals can. The respiratory physiology of underwater swimmers was also investigated. By studying oxygen consumption and determining the coefficient of oxygen utilization, it was found that an underwater swimming rate of 0.7 knots was most efficient although the efficiency did not exceed 5.1%.

Analgesics - The separation of pain relieving and addicting properties continues to be a goal of NIAMD's chemists and biologists. A number of new compounds were prepared, some of which appear promising. One compound in particular (5-(m-hydroxyphenyl) 2-methylmorphan) had analgesic activity equal to morphine in animals but without the side effects characteristic of morphine. Quantities of the compound are being prepared for addiction studies. Numerous contributions were made to the chemistry and structure of compounds related to analgesics. Synthesis of potential new analgesic agents related to thebaine, morphine, and methodone have received particular attention.

Shock - Important additional data has been collected in man establishing the safety and efficacy of oral saline and soda in the treatment of burn shock.

In animals studies, preliminary data suggests that the timing of colloid therapy in relation to swelling in injured areas may be quite important in therapy. The simultaneous use of the synthetic plasma expanders, dextran and PVP, is being studied in dogs to determine compatibility, effects on renal hemodynamics, possible tissue localization and damage.

Microbes - NIAMD's pathologists have cooperated with numerous scientists in other institutes in various infectious disease investigations. Other studies are being conducted to concentrate, separate, and purify viruses by chromatographic techniques. Several drugs have been found which are superior to sulfones in treating mouse leprosy. A saturated solution of sulfamethazine in drinking water appears to control coccidiosis in rabbits. A booklet was published on the identification of helminths and protozoa in laboratory animals. The incidence and pathological features of histoplasmosis in dogs and cats was determined.

Microscopy - The visualization of living and dead matter at high magnifications is an integral part of many research programs in this institute. Considerable progress has been made in devising or adapting chemical reactions to obtain more precise localization and identification of substances in tissues. For example, it was found that nerve cell melanin is different from other melanins. Histochemical enzyme localizations indicate a diversity of function as well as morphology in the several segments of the nephron. Some progress has been made in devising a histochemical technique to localize thyroxin. Utilizing the very high magnifications of the electron microscope, it was found that a bacteriophage had a capsule composed of striated fibers rather than the expected gel. Certain bacteria revealed cell walls of perfectly ordered spherical macromolecules with flagella composed of helical structures showing an underlying regularity in macromolecular structure.

Toxicology - Iodates are a desirable vehicle in iodizing table salt where heat and himidity make iodide impractical. However, the safety of iodates is not established. NIAMD scientists have concluded the first portion of a study which, by extrapolating animal data to man, shows a large margin of safety in spite of the fact that iodates are more toxic than iodides. Thiosulfate and bicarbonate are effective in reducing iodate toxicity. Additional studies of iodates, particularly as to their methemoglobin producing tendency, will be necessary before final conclusions as to safety for man can be predicted. Toxic doses of iodates were shown to damage the parietal cells of the stomach and the retina. A survey of the clinical toxicity of antibiotics has been made and prepared for publication. A book on the toxicity of halogenated hydrocarbons has been submitted for publication.

Analysis of NIH Program Activities

January-December 1954

National Institute of Arthritis and Metabolic Diseases
Extramural Activities

The National Institute of Arthritis and Metabolic Diseases supports four extramural activities: 1) Grants-in-Aid for Research, 2) Research Fellowships, 3) Traineeships, and 4) Training Grants. The last named program was activated during the last two months of the year and at the end of the year no grants had been made.

Research Grants

At the end of the year there were a total of 428 active research projects representing a sum of $4,020,712. The distribution of these projects is as follows: Arthritis-89, Diabetes-69, Nutrition-35, Diseases of Blood-24, Allergy-12, Diseases of the Liver-11. Under the heading of Metabolism the following areas were represented: Adrenal Gland and Hormones-24, Thyroid Gland and Hormones-23, Kidney 14, Pituitary Gland and Hormones-13, Digestive Tract, including Pancreas,-13, basic studies including Enzyme, Protein, Water, Mineral, Phospholipid and Vitamin studies-64. The remaining miscellaneous studies have to do with general endocrine disturbances, growth and development, and pregnancy.

During the past year particular attention has again been paid to stimulation of research in the fields of diabetes and arthritis. These areas have been particularly neglected in the past and it is interesting to note that funds from this Institute alone gave more support during 1954 to arthritis and rheumatic diseases than did all government and private agencies in 1950. In 1951 the National Institute of Arthritis and Metabolic Diseases supported 12 arthritis

projects in 8 states. This past year 89 projects have received support. These are located in 25 states and the District of Columbia. At the Interim-meeting of the American Rheumatism Association held in Bethesda in November 1954, over half of the papers presented were the result of studies supported by the funds of this Institute. It is, of course, apparent that we have at the present time no knowledge of the precise steps toward the ultimate solution of the problem of arthritis. It is possible, in fact--likely, that many projects that receive their support not only from this Institute but from other sources, which at present have no apparent relationship to arthritis may prove to be the key steps in the ultimate victory over this disease. For these reasons our present classifications are obviously superficial.

Accomplishment Highlights

1. Many phases of clinical arthritis are being studied. The problem of getting the crippled arthritic back to work is one supported by this Institute which has been the subject of study. By means of intensive rehabilitation procedures, in 17 patients severely disabled by arthritis, 13 have been discharged from the hospital; 6 of these are now self-sufficient. One has been job-placed. The other 7 are partially self-sufficient. Of 21 less severely disabled patients, all have been discharged from the hospital and 16 are self-sufficient, while 5 are partially so with an average increase of 16% in function. Seven of these last 21 patients have full-time jobs.

2. Of the projects dealing with fundamental studies of connective tissue, one in particular has brought out some interesting findings. A "building block" of connective tissue is the substance known as collagen. By chemical treatment of this material it has been possible to visualize through the electron-microscope

changes in its structure. Treatment with one chemical apparently dissolves the material, but it can be returned to its previous complicated physical appearance by treatment of this solution with another chemical substance.

3. Advances have also been made in the study of joint fluid. In the past, all studies of joint fluid have been done on fluid which has been removed either from animals or from humans with damaged joints or from humans at autopsy. It has been thought to be impossible to be able to collect a sufficient amount of normal human joint fluid for physical and chemical studies. Using a simple technic, a group of investigators have finally hit upon a method to obtain fluid from the joints of normal living human subjects and have discovered in it a hitherto unidentified substance which is not present in the joint fluid of patients with rheumatoid arthritis nor in normal human serum. Studies to identify and learn the significance of this material are under way.

4. In the field of diabetes considerable attention is being paid to the natural course of the disease over a long period of time with particular reference to some of the degenerative complications. By these studies new knowledge is being gained of the natural course of the disease under various types of treatment. One team of investigators has studied 486 diabetic patients who developed diabetes during childhood, and who have had the disease for up to 30 years. Forty of these patients have died, and of those, infection or diabetic acidosis have accounted for most of the deaths in patients who have had the disease less than ten years. Heart and kidney disease accounted for 40% of the deaths in patients who had had diabetes more than ten years.

5. The majority of individuals who develop diabetes in adult life are obese. Better understanding of the disturbances of the metabolism of fat and

sugars is important in understanding better the nature of diabetes. Such a study is being carried out on a grant from this Institute. Dogs and rabbits are made diabetic and the metabolism of glucose and fat is being studied by our most advanced technics.

6. It has been possible to make insulin radio-active. With this advance, a more complete understanding of the way insulin acts and its distribution and metabolism is available. Intensive studies along these lines are being supported by grants to several institutions.

7. The importance of proper nutrition in pregnancy has long been recognized. Only recently, however, has it been demonstrated that deficiencies of certain vitamins in the diets of pregnant animals have been found to cause profound results in the offspring. For example, lack of vitamin A in the diet causes malformations of the eye, the heart, the diaphragm and the urogenital organs. Vitamin D deficiency in the mother causes a great variety of changes in the bones of the offspring.

Research Fellowships

Forty-three research fellowships were awarded during the year.

Traineeships

Seventy-four trainees in arthritis, diabetes, and metabolic diseases received awards. In addition, one clinical fellow in rehabilitation was appointed.

Analysis of NIH Program Activities

January-December 1954

National Institute of Arthritis and Metabolic Diseases
Clinical Investigations

Adrenal Steroids

The past year has witnessed in this country and in Europe a resurgence of interest and vigorous research activity in the chemical, physiological and clinical aspects of adrenocortical steroids. The isolation and identification of aldosterone, the synthesis of radioactive hydrocortisone and cortisone acetate, and the development of better methods for the biochemical analysis of 17-hydroxycorticosterones were chiefly responsible for these renewed efforts in medical scientific research. Scientists in Clinical Investigations of NIAMD have actively participated in this fresh assault.

Utilizing radioactive hydrocortisone and improved methods for biochemical analysis of 17-hydroxysteroids and 17-ketosteroids developed in this laboratory, the rate of endogenous production, turnover rate, physiological disposition and metabolic fate of hydrocortisone were determined both in the experimental animal and in man during health and disease. It was discovered that the adrenal cortex in normal man produces approximately 40 mg. of hydrocortisone daily, that the metabolic pool consists of 3 to 4 mg. and that this pool is turned over approximately ten times a day. Hydrocortisone in either pharmacological or physiological (trace) amounts was found to have a mean half-life in plasma following its intravenous infusion into normal subjects of 115 minutes. Cortisone disappeared from the plasma twice as rapidly as hydrocortisone (65 minutes). The rate of disappearance of hydrocortisone from the plasma was markedly delayed in patients with liver disease and was much accelerated in patients with thyrotoxicosis. Isotopic

hydrocortisone administered to normal man in large or trace amounts, intravenously or orally was very rapidly excreted, almost entirely in the urine. Fifty percent appeared in the urine with the first six hours, additional 30% in the next 18 hours and 10% more in the following 24 hours. Only 5% appeared in the feces. Thus 95% of the administered radioactivity was recovered. No isotope was demonstrated after 96 hours and none appeared in the expired carbon dioxide.

The biological mechanism for inactivation of hydrocortisone and cortisone in mammals has been defined by Institute scientists. Enzymes have been isolated in the granule-free cytoplasm of the rat liver which convert adrenal steroids to their inactive "tetra-hydro" form. Two enzyme systems are involved in this process. Enzyme I reduces cortisone to dihydrocortisone, possesses low activity and requires TPNH as a co-factor. Enzyme II completes the process and mediates the reduction of dihydrocortisone to tetrahydrocortisone. The second enzyme can utilize either DPNH or TPNH as a co-factor and in contrast to the first enzyme is very active and lacks specificity, reducing other dihydrosteroids besides dihydrocortisone.

In addition, the manner in which the reduced tetrahydro corticosteroids are subsequently conjugated as their glucuronides has been elucidated. Uridine diphosphate glucuronic acid has been found to be the active glucuronide donor for this process. This co-factor is present in mammalian liver and with the aid of an enzyme found in the microsomes of hepatic cells transfers its glucuronic acid to the steroid. Purification of the enzyme and studies as to its specificity are under investigation at present. It is apparent that uridine diphosphate glucuronic acid serves as a co-factor in the formation of many other glucuronides and is therefore of paramount biologic importance.

Steroid chemists have repeatedly demonstrated than an exquisite relationship exists between the chemical structure of adrenal steroids and their physiological properties. Clinical investigators found, in addition, a very close correlation between the structural formula and the therapeutic capacities of these hormones. The addition, removal or transfer of a single atom or substituent in the corticosteroid molecule may effect a drastic change in its clinical effects or indeed its therapeutic potency.

Unremitting efforts have been made by the synthetic chemists to produce a steroid possessing high anti-inflammatory or antirheumatic potency. Two such compounds, metacortandralone and metacortandracin, were submitted to NIAMD for clinical trial and evaluation in August and October 1954. Tested in 15 patients with rheumatoid arthritis who failed to improve with cortisone, hydrocortisone, corticotropin, gold compounds or phenylbutazone, the new steroids induced a spectacular clinical response in all but two. These two patients had far advanced arthritis with irreversible destructive changes in many joints. Even they showed definite but not dramatic improvement. The new steroids were found to have 3 to 4 times the potency of cortisone or hydrocortisone. This enhanced potency was not accompanied by a corresponding increase in the severity or frequency of undesirable side-effects. It was demonstrated that these steroids possessed the physiological properties of adrenocortical hormones. It is planned to subject to clinical trial at NIAMD additional steroids as they are synthesized or isolated provided there is evidence to believe from preliminary studies on animals that they may have anti-inflammatory properties.

Connective Tissue Metabolism

Although rheumatoid arthritis is clinically the most important of the diseases affecting joints little is known today of its underlying pathogenesis. The structures of joints are made up of connective tissue which contains characteristic sugars rich in hexosamine. Institute scientists have discovered that isolated fragments of connective tissue retained their capacity to produce hexosamines. They have further shown that the concentration of hexosamine in connective tissue is directly influenced by hormones secreted by the thyroid and anterior pituitary glands. They have also collected important information concerning the nature of some of the changes observed in disease processes and may lead to a better understanding of the pathogenesis of certain rheumatic diseases, especially rheumatoid arthritis. New techniques have been devised during the course of these studies which may help provide more information along these lines.

Specific Serological Test for Rheumatoid Arthritis and the Nature of the Factors Involved

A test proven useful in the diagnosis of rheumatoid arthritis depends upon the capacity of serum from such patients to agglutinate sensitized sheep red blood cells. This serological test has been refined so that at present it is positive in about 90% of the patients. In the course of study yielding a specific agglutinating factor in serum from arthritic patients it was discovered that this serum lacks an agglutination inhibitor found in the euglobulin fraction of normal plasma protein. The activity of this inhibitor has been matched with a simple synthetic polypeptide which, when injected into patients, partially reverses the agglutination reaction. This abnormality in the constitution of the plasma proteins in patients with rheumatoid arthritis is being further explored to ascertain whether, by its reversal, a remission in the disease process can be induced.

Anemia

The life expectancy of the red blood cell, whether in a normal or in an anemic subject, has in the past been estimated by the Ashby technique. This procedure, involving a transfusion of blood from another donor, involves hazard of transfusion reaction as well as homologous serum hepatitis. Institute scientists have perfected a far simpler and safer technique involving the withdrawal of a small sample of the patient's blood, tagging of these red cells with radioactive chromium, and reinjection of these labeled red blood cells into the same subject. Clearly the understanding of the mechanism leading to anemia, in any circumstance, requires exact knowledge of the viability of the red cells, and this knowledge is now readily available. A hitherto unsuspected difference between men and women in this regard has already been brought to light.

Diabetes

The attack upon diabetes has been multidisciplined. In this disease, attributable to a relative or absolute deficiency of insulin, the most prominent disturbance metabolically is of the utilization of body sugars by certain tissues. Improved diagnosis, prophylaxis and therapy must rest upon an increasingly precise understanding of the defects underlying the disease. At a purely chemical level the reactivities and structural relationships of the several sugars are being studied. At an enzymological level, the metabolic pathways whereby sugar is converted into other products and is ultimately burned in the body are being investigated. A novel route of glucose oxidation, hitherto but vaguely outlined, has been systematically explored and explained by Institute scientists. The intimate mechanism of sugar storage in the animal is under investigation by new techniques. Endocrinological studies are directed toward a clearer understanding of the

relationship of insulin and its antagonists, and a program has been initiated designed to clarify the nature of anti-insulin agents which occur in the blood of some diabetic patients. Finally the metabolism of those cells of the pancreas responsible for insulin production is to be studied, in the hope of finding an explanation for their curious and unique function.

Thyroid Function and Disease

It has been found by Institute scientists that the normal liver is capable of removing a large amount of the protein bound iodine circulating through it as determined by comparison of arterial and hepatic venous blood. Thyroid homogenates have been found to have the ability to utilize iodide converting it to monoidotyrosine and, especially, to an intermediate iodine form which is extractable by carbon disulfide. These studies represent new approaches to several aspects of thyroid physiology and disease. These include the mechanism of hormone synthesis in the normal and diseased thyroid, the role of the liver in thyroid hormone metabolism, and the role of the specific thyroxine-binding protein in thyroid physiology.

P.C. - 1

Analysis of NIH Program Activities

Project Description Sheet

NIAMD
INSTITUTE

2. Laboratory of Biochemistry and Nutrition
LABORATORY OR BRANCH

Biochemistry & Physiology of Nutrition
SECTION

4. --
LOCATION (IF OTHER THAN BETHESDA)

NIAMD-62113-1
SERIAL NO.

Antibiotics and Vitamin C in B Vitamin Deficiencies
PROJECT TITLE

E. G. McDaniel
PRINCIPAL INVESTIGATOR

F. S. Daft
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Many workers have shown the profound effect of antibiotics in altering an organism's requirement for vitamins. In this laboratory it has been shown (F.S. Daft) that large amounts of dietary vitamin C have a similar effect. These studies are being continued to define the scope and mechanism of these effects.

In dogs it has been shown that 5% dietary vitamin C prevents or delays deficiencies of riboflavin and pantothenic acid. In rats 5 or 10% ascorbic acid, or low levels of penicillin in the diet improve growth, increase survival and tend to prevent dermatitis in B_6 deficiency. Dietary aureomycin had an effect opposite to penicillin in B_6 deficiency. Penicillin would not prevent the deleterious effects of aureomycin.

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Analysis of NIH Program Activities

Budget Data Sheet

NIAMD-62113-1
SERIAL NO.

BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	10,500	2/3	2/3	1 1/3	2/3	2/3	1 1/3	
FY 1956	10,500	2/3	2/3	1 1/3	2/3	2/3	1 1/3	

BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	TECHNICAL ASSISTANCE	☐

IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

None

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

.C. - 3

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

NIAMD-62113-1
SERIAL NO.

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

P.C. - 1

Analysis of NIH Program Activities

Project Description Sheet

NIAMD
INSTITUTE

2. Laboratory of Biochemistry and Nutrition
LABORATORY OR BRANCH

Biochemistry & Physiology of Nutrition
SECTION

4. --
LOCATION (IF OTHER THAN BETHESDA)

NIAMD-62113-2
SERIAL NO.

Diabetes and Niacin Metabolism Studies
PROJECT TITLE

E. G. McDaniel and W. H. Sebrell
PRINCIPAL INVESTIGATOR(S)

None
OTHER INVESTIGATORS

PROJECT DESCRIPTION - Studies with the B vitamin niacin are being continued because of its importance in health and in metabolic reactions.

A. Alloxan diabetic rats appear to be unable to convert tryptophan to niacin as judged by their failure to excrete normal levels of urinary N^1-methylnicotinamide (NMN) following tryptophan (T) dosage, although they do respond following dosage with niacin, niacinamide, or NMN. Control of diabetes with insulin leads to a normal T to NMN conversion. Feeding of fructose to diabetic rats ameliorated the signs of diabetes but did not improve the T to NMN conversion. The conversion of niacinamide to NMN appears to be impaired in some diabetic rats but not to the extent the T to NMN conversion is affected. Administration of T to diabetic rats resulted in elevated blood sugar curves.

Rats made diabetic by other means will be investigated to determine whether they too show an impaired T to NMN conversion. Attempts will be made to determine the nature of this metabolic defect more precisely. Experiments are underway to find whether human diabetics exhibit a defect in T metabolism similar to the rat.

B. 3-Acetylpyridine (3-AP) (a niacin antagonist) studies have been continued in dogs and rats. The dog studies have shown that 3-AP acts either to replace niacin or as an antagonist depending on dosage and the nutrition of the dog

with respect to niacin. Normal and niacin deficient dogs convert 3-AP to niacin as shown by NMN excretion and the prevention and treatment of blacktongue. Niacin deficient dogs appear less able to make this conversion. Marked toxic symptoms, including multiple paralyses, sometimes result when 3-AP is given to niacin deficient dogs, or with large doses to normal dogs.

Pathological examinations are being conducted, especially on brain and spinal cord, to determine the basis for the paralyses noted above.

In rats, experiments have been conducted to determine whether the lack of ability to convert 3-AP to niacin is specific for niacin deficiency. To date the conversion of 3-AP has been tested in riboflavin, pyridoxine, thiamine, pantothenic acid and niacin deficiencies. Only with niacin deficiency were the animals unable to make the conversion.

C. The role of corn in the etiology of pellagra is being approached by studying the effect of alkali treatment on the "availability" of niacin and the general nutritive value of corn in studies with dogs. Corn is being treated under various conditions with Na, K or Ca hydroxides. Under appropriate conditions any of these treatments seems to increase the supply of niacin as judged by NMN excretion. This finding will be checked by studies on the prevention of blacktongue in dogs. Treatment of whole corn with lime (as in the making of Mexican Tortilla) did not produce the same effect mentioned above.

.C. - 2

Analysis of NIH Program Activities

Budget Data Sheet

NIAMD-62113-2
SERIAL NO.

BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	14,300	1/3	2 1/3	2 2/3	1/3	2 1/3	2 2/3	
FY 1956	14,300	1/3	2 1/3	2 2/3	1/3	2 1/3	2 2/3	

BUDGET ACTIVITY:

RESEARCH ☒
REVIEW & APPROVAL ☐
ADMINISTRATION ☐
TECHNICAL ASSISTANCE ☐

IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

None

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

P.C. - 3

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

NIAMD-62113-2
SERIAL NO.

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Niacin and Anti-Niacin Activity of 3-Acetylpyridine in Dogs. E. G. McDaniel, J. M. Hundley and W. H. Sebrell, J. Nutrition (in press) (1955).

LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

Analysis of NIH Program Activities

Project Description Sheet

NIAMD
INSTITUTE

2. Laboratory of Biochemistry and Nutrition
LABORATORY OR BRANCH

Biochemistry & Physiology of Nutrition
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

NIAMD-62113-3
SERIAL NO.

Vitamin and Amino Acid Metabolism
PROJECT TITLE

F. S. Daft
PRINCIPAL INVESTIGATOR(S)

M. Gray, M. L. Kunde
OTHER INVESTIGATORS

PROJECT DESCRIPTION

A. Vitamin Sparing Factors

Previous work has shown that large amounts of dietary vitamin C or small amounts of certain antibiotics have the ability to decrease markedly the rat's requirement for a variety of B vitamins. Current work is directed toward elucidating the mechanisms of these effects using various routes of administering the substances, vitamin balance techniques, and dietary manipulations. It has been found that penicillin administered parenterally finds its way into the gastro-intestinal tract via the bile. Technics have been developed to divert the biliary secretions from the intestinal tract as an approach to determining whether antibiotics exert their vitamin sparing effect in the G-I tract or in the tissues. Other studies have shown that whatever the mechanism may be, large amounts of dietary vitamin C result in an increased supply of certain B vitamins in tissues. This work may have considerable significance in elucidating the various factors which influence vitamin requirements, as well as throwing considerable light on vitamin metabolism.

B. Histidine-Folic Acid Metabolism

Previous work has shown that folic acid deficient rats excrete a urinary compound which has been isolated and tentatively identified as formimino glutamic

acid and that this compound arises from the amino acid histidine. Current work is directed toward defining the conditions under which this compound is excreted, especially with load tests of histidine, as an approach to develop a biochemical test for folic acid deficiency and to the mechanisms which prevent folic acid deficient animals from completely metabolizing histidine.

C. Metastatic Calcification in Mice

C3H mice fed a purified low protein diet develop calcified lesions in heart, muscle, arteries and lungs. The influence of various dietary supplements and dietary modifications are being studied to determine the etiology and pathogenesis of this syndrome. It has been shown that calcification is greatly lessened by increasing dietary protein and by certain supplements. These experiments may shed light on certain types of arteriosclerosis and possibly on unknown nutritional factors.

Analysis of NIH Program Activities

Budget Data Sheet

NIAMD-62113-3
SERIAL NO.

BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	19,200	-	3½	3½	-	3½	3½	
FY 1956	19,200	-	3½	3½	-	3½	3½	

BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

Drs. Tabor and Silverman and Mr. Bakerman - NIAMD 62125-76 and NIAMD-62116-29

Dr. B. Highman - NIAMD - 62112-62

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

P.C. - 3

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

NIAMD-62113-3
SERIAL NO.

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

"Excretion of a Histidine Metabolite by the Rat", M. Silverman, H. A. Bakerman, and F. S. Daft, Proc. Soc. Exper. Biol. Med. 87: 451 (1954).

"Isoglutamine and the Growth of Lactobacillus Arabinosus" M. Silverman, M. K. Romine and F. S. Daft, J. Bact. 68: 98 (1954).

"Pantothenic Acid" Parts of Chapter 11 in Sebrell and Harris's "The Vitamins", G. M. Briggs and F. S. Daft, Vol. II., pp. 628-630, 633-669, 682-687, Academic Press, Inc., New York (1954).

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7 LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

P.C. - 1

Analysis of NIH Program Activities

Project Description Sheet

NIAMD
INSTITUTE

2. Laboratory of Biochemistry and Nutrition
LABORATORY OR BRANCH

Biochemistry & Physiology of Nutrition
SECTION

4. --
LOCATION (IF OTHER THAN BETHESDA)

5. NIAMD-62113-4
SERIAL NO.

6. Nutritional Improvement of Cereals
PROJECT TITLE

7. J. M. Hundley
PRINCIPAL INVESTIGATOR(S)

8. R. B. Ing
OTHER INVESTIGATORS

9. PROJECT DESTRIPTION

Previous animal experiments in this and other laboratories have shown that amino acids lysine and threonine significantly improve the nutritional value of rice, wheat, rye, bread and certain "poor" diets typical of Puerto Rico and India.

Current work is directed toward finding foods which constitute good sources of lysine and threonine to supplement these cereals. Particular attention is devoted to sources of threonine since lysine can be produced cheaply by synthetic means. A dried alga (Scenedesmus obliquus) has appeared very promising in preliminary tests.

The significance of this work relates to the possible improvement of the predominantly cereal diets consumed in large sections of the world where protein undernutrition is especially prevalent. The effect of lysine and threonine supplements in human diets is being explored (see item 13).

R.P.C. - 2

Analysis of NIH Program Activities

Budget Data Sheet

NIAMD-62113-4
SERIAL NO.

BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	12,800	½	1 1/6	1 2/3	½	1 1/6	1 2/3	
FY 1956	12,800	½	1 1/6	1 2/3	½	1 1/6	1 2/3	

BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

Dr. R. W. Krauss, University of Maryland (Algae studies)

Clinical Studies of Lysing and Threonine Supplemented Rice Diets (with Dr. H. Sandstead) NIAMD - 62113-105

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

.C. - 3

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

NIAMD-62113-4
SERIAL NO.

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1

Analysis of NIH Program Activities

Project Description Sheet

NIAMD
INSTITUTE

2. Laboratory of Biochemistry and Nutrition
LABORATORY OR BRANCH

Biochemistry & Physiology of Nutrition
SECTION

4. --
LOCATION (IF OTHER THAN BETHESDA)

NIAMD-62113-5
SERIAL NO.

Nutritional Aspects of Growth and Longevity
PROJECT TITLE

J. M. Hundley
PRINCIPAL INVESTIGATOR(S)

R. B. Ing, Dr. O. Mickelsen
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Animal Studies

The purpose of the study is to relate rapidity of growth to the composition of the body, to the development of disease and to longevity. Various diets are fed to produce planes of growth varying from severe retardation to above normal. Two strains of animals are being used, one is naturally slow growing which is not expected to become obese, and the other is a rapidly growing strain which is expected to become obese.

The study is expected to require 3 years and has not progressed far enough to yield major findings except to state that the methods employed have yielded the desired planes of growth as determined by carcass analysis. A method has been developed to estimate body fat in rats by specific gravity.

The significance of the project relates to the influence of diet in obesity and the degenerative diseases and to influences of growth during "childhood" to eventual adult health and longevity.

Clinical Studies

Height-weight-age-sex-color-economic class data have been obtained on 10,975 6 to 8 year old children who were in the public schools in Philadelphia between

1925 and 1949. The data have been analyzed with the following resutls: Children from good socioeconomic areas were consistently taller and heavier than those from less favored areas. All groups of children showed a distinct secular increase in growth. Alterations in growth patterns and in attained heights and weights were found in the depression years of the 1930's.

The significance of this study relates to the possibility of using periodic height-weight measurements on children to yield a continuing index of nutritional status in this country.

It is planned to broaden the study to relate the pattern of growth during childhood to adult obesity, disease and longevity.

.C. - 2

Analysis of NIH Program Activities

Budget Data Sheet

NIAMD-62113-5
SERIAL NO.

BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	13,600	½	2 2/3	3 1/6	½	2 1/3	2 5/6	
FY 1956	20,300	½	3	3½	½	3	3½	

BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

Dr. R. Weaver and R. C. Taber - Philadelphia Board of Education (Studies with Children)

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

NIAMD-62113-5
SERIAL NO.

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

"Diseases Due to Vitamin Deficiency and Malnutrition" W. H. Sebrell, W. M. Yater and J. M. Hundley. Chapter 14 in Yater's Fundamentals of Internal Medicine, 4th Edition, Appleton-Century-Crofts, Inc., New York (1954).

"Malnutrition" W. H. Sebrell and J. M. Hundley, Chapter 13 in Stieglitz's Geriatric Medicine, 3rd Edition, J. B. Lippincott Co., Philadelphia (1954).

"Niacin" J. M. Hundley, Chapter 10 in Sebrell and Harris's The Vitamins, Academic Press Inc., New York (1954).

"The Importance of Nutrition" J. M. Hundley, J. Home Econ. 46: 307 (1954).

"Evaluation of Nutritional Status of Populations - Nutrition Survey Methods", W. H. Sebrell and J. M. Hundley in "Symposium on Nutrition Adequacy and Status", National Research Council, Washington, D. C. (in press) (1954).

"Joseph Goldberger - A biographical Note", J. M. Hundley, Public Health Reports 68: 738, Aug. (1953).

"Preventive Geriatrics, Comments on Nutrition", J. Michigan State Med. Soc. 53, 524, May (1954).

"Balanced, Varied Diets Are Basis for Good Nutrition" Condensation of a Speech, J. M. Hundley, Pub. Health Reports 69: 855, Stept (1954).

"Nutrition and Public Health" J. M. Hundley, Public Health News 35: 423, Nov., (1954).

"Significance of Blood Levels of Various Nutrients" J. M. Hundley, Proc. Eighth Community Nutrition Institute, Syracuse Univ. (In press) 1954.

"Nutritional Needs of Institutionalized Patients" J. M. Hundley, J. Am. Pub. Health Assoc. (In press) (1955).

"Niacin and Anti-Niacin Activity of 3-Acetylpyridine in Dogs" E. G. McDaniel, W. H. Sebrell and J. M. Hundley, J. Nutrition (In press) (1955).

LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Fleming Award (Dr. Hundley)

Councillor to American Institute of Nutrition (Dr. Hundley)

R.P.C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Biochemistry and Physiology of Nutrition
SECTION

4. Bethesda
LOCATION

5. NIAMD-62113-6
SERIAL NUMBER

6. Effect of hormones on muscle and pelt proteins and on carbohydrate metabolism
PROJECT TITLE

7. Dr. Robert O. Scow
PRINCIPAL INVESTIGATOR

8. Susie N. Hagan
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To determine the influence of hormones on carbohydrate metabolism and on the proteins in muscles and pelts of animals of various ages.

Methods Employed: Various endocrine glands are removed from young experimental animals (rats, mice, guinea pigs). Some of these animals are treated with a variety of hormone preparations. At the end of the experiment the animals are killed and appropriate measurements are made. Selected muscles are rapidly excised, frozen in carbon dioxide, powdered, and then extracted with a salt solution. Purified proteins fractions are prepared by precipitation procedures. Pelt proteins are extracted using a variety of eluting agents.

Glucose tolerances (oral and intravenous) were made on normal and thyroidectomized rats, some of which had been force-fed to increase their body weight. The food intake of some normal rats was restricted so that the rats weighed the same as the thyroidectomized animals.

Major Findings: Thyroxine has a marked influence on protein formation as shown by the increase in body weight and muscle protein content of hypophysectomized rats injected with this hormone.

Both oral and intravenous glucose tolerances of thyroidectomized rats were impaired. There was no effect of food intake or body size on the oral and intravenous tolerance curves in normal and thyroidectomized rats. The maximum blood glucose level in thyroidectomized rats during the oral test was 50% above that of normals, probably due to an

9. PROJECT DESCRIPTION - Continued

impaired rate of glucose removal from the blood. The blood glucose removal rate during the intravenous test was slower than normal, presumably due to a delay in urinary glucose excretion.

Preliminary evidence indicates that when young rats are not given any food for 68 hours, there is a substantial decrease in the percentage of myosin in muscle, with none of the other muscle proteins showing a similar change.

Significance to NIAMD Research: Since a number of metabolic diseases are associated with marked disturbances of body protein formation, it is important to know the factors that influence muscle growth and formation. Disturbances in the growth of collagen, one of the proteins studied in this project, occurs in arthritis and in a number of other diseases.

Proposed Course of Project: Muscle, pelt, and carcass analyses will be performed on hypophysectomized rats treated with growth hormone, testosterone, or both, and on untreated control animals. The influence of testosterone on the muscle protein of gonadectomized rats will be studied. Studies will be made on the effects of fasting, both the complete withdrawal of food and semi-starvation, on the changes in muscle protein composition.

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD-62113-6
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	17,300	1	1 1/3	2 1/3	1	1 1/3	2 1/3	
FY 1956	17,300	1	1 1/3	2 1/3	1	1 1/3	2 1/3	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

Arthritis and Rheumatism Branch, CI, NIAMD-62131-95
Radiation Branch, NCI-
Endocrinology Branch, NCI-

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

None

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD-62113-6
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Scow, R. O. "Effect of Thyroxine on the Weight and Composition of Muscle, Pelt and other Tissues in Young Hypophysectomized Rats". Endocrinology 55: 344, 1954

Scow, Robert O., and Jerome Cornfield. "Effect of Thyroidectomy and Food Intake on Oral and Intravenous Glucose Tolerances in Rats". Am. J. Physiology 179: 39, 1954

Scow, Robert O., and Jerome Cornfield. "Quantitative Relation between the Oral and Intravenous Glucose Tolerance Curves". Am. J. Physiology. In press (1955)

Scow, Robert O., and Susie N. Hagan. "Effect of Testosterone Propionate on Myosin, Collagen, and Other Protein Fractions in Striated Muscles of Gonadectomized Male Guinea Pigs". Am. J. Physiology. In press (1955)

Boas, Norman F., and Robert O. Scow. "Apparent Exophthalmos in the Rat Following Cortisone Treatment or Thyroidectomy". Endocrinology 55: 148, 1954.

Wollman, S. H., and R. O. Scow. "Comparison of Thyroid Lobes, Autotransplanted and in situ, in the Rat: Growth and I^{131} Uptake". J. Nat. Cancer Inst. In press (1955)

Wollman, S. H., and R. O. Scow. "Dependence of Ratio of Radio-iodide Concentrations in Thyroid Gland and Serum on Serum Iodide Concentration: With Propylthiouracil". Endocrinology 55: 828, 1954.

Wollman, S. H., and R. O. Scow. "Dependence of Ratio of Radio-iodide Concentrations in Thyroid Gland and Serum on Serum Iodide Concentration: Without Propylthiouracil". Endocrinology 55: 837, 1954.

Wollman, S. H., and R. O. Scow. "Effect of Various Goitrogens and of Dose of Propylthiouracil on the Ratio of Radio-iodide Concentrations in the Thyroid Gland and Serum in Mice". Endocrinology. In press (1955)

Scow, R. O., and M. A. Greer. "Effect on the Thyroid Gland of Experimental Alteration of the Level of Circulating Thyroxine in Mice with Heterotopic Pituitaries". Endocrinology. In press (1955)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Biochemistry and Physiology of Nutrition
SECTION

4. Bethesda
LOCATION

5. NIAMD-62113-7
SERIAL NUMBER

6. Nutritional significance of vitamin B_{12}, methionine, choline, and related compounds for the chick
PROJECT TITLE

7. Dr. M. R. Spivey Fox
PRINCIPAL INVESTIGATOR

8. Dr. G. M. Briggs; Ligia O. Ortiz
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To determine the function, interrelationships, and requirement of these nutrients for optimal nutrition of the chick under various dietary conditions.

Methods Employed: A deficiency of each of these nutrients has been produced by dietary omission and/or use of a specific antagonist. The effect of various nutrients in relieving or intensifying the severity of each deficiency has been studied. The effect of these dietary alterations upon gross and histological structure as well as chemical composition of certain tissues has been determined in many of these experiments.

Major Findings: (1) It has been shown previously in this laboratory that the severity of the vitamin B_{12} deficiency in young chicks could be markedly increased by inclusion of 20% fat in an all-vegetable diet free of B_{12}. Five percent of an amino acid mixture (based on the composition of casein, but with methionine omitted) caused further growth depression of B_{12}-deficient chicks fed the high fat diet.

(2) The chick's requirement for B_{12} with the high fat diet was 100 µg./kg. of diet, whereas optimal growth was obtained with 5 µg. B_{12}/kg. of diet when no fat was added.

(3) In the absence of dietary B_{12} the concentration of B_{12} in the liver at 4 weeks of age was the same (10-50 µg./g. of liver) with either 4 or 24% fat in the diet. The quantity of B_{12} in the liver

9. PROJECT DESCRIPTION - Continued

increased with dietary level and was not affected by high fat in diet. High fat appears, therefore, to increase the chick's metabolic requirement for B_{12} and not to affect absorption.

(4) The growth depression in the absence of B_{12} could be overcome by supplementary B_{12}, methionine, or the combination of 5% casein plus 0.2% choline (not by either alone). Substances which improved growth of B_{12} deficient chicks did not alter B_{12} concentration in the liver.

(5) The total fat and phospholipid concentrations in the liver were normal in the B_{12}-deficient chick.

(6) Addition of ethionine (the ethyl analogue of methionine) to a complete synthetic-type diet caused growth depression, hypertrophy and fatty infiltration of the liver of young chicks.

(7) The adverse effects of ethionine could be overcome with supplementary methionine, but not with elemental sulfur or high B_{12}. Cystine increased ethionine toxicity whereas additional choline had a variable effect.

Significance to NIAMD Research: Provides basic information on the nutritional importance of these key nutrients that is applicable to other studies using the chick and may be of importance to man. The chick appears to be particularly well suited to the study of vitamin B_{12}, the nutrient involved in pernicious anemia in man.

Proposed Course of Project: To continue along the same lines as well as to explore in more detail the biochemical alterations associated with nutritional changes involving these nutrients.

R.P.C. - 2
December 1954

Analysis of NIH Program Activites

Budget Data Sheet

10. NIAMD-62113-7
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	23,600	5/6	1	1 5/6	5/6	1	1 5/6	
FY 1956	26,600	1	1	2	1	1	2	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

Laboratory of Pathology, NCI-
Arthritis and Rheumatism Branch, CI, NIAMD-62131-97

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD-62113-7
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Spivey, M. R., G. M. Briggs, and L. O. Ortiz. Effect of diets high in fat or protein on vitamin B_{12} deficiency in non-depleted chick. Proc. Soc. Exp. Biol. Med. 85: 451 (1954).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Biochemistry and Physiology of Nutrition
SECTION

4. Bethesda
LOCATION

5. NIAMD- 62113-8
SERIAL NUMBER

6. Studies on the nutrition of the chick and the mouse.
PROJECT TITLE

7. Dr. G. M. Briggs
PRINCIPAL INVESTIGATOR

8. Dr. M. R. Spivey Fox; Ligia Ortiz
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To gain more information of a fundamental nature on folic acid, unidentified factors, fat, vitamin E, lactose, and other nutrients in the nutrition of the chick and the mouse so that this information may be applied to and compared with the nutrition of other laboratory animals with eventual application to man.

Methods Employed: By the use of highly purified, semi-synthetic diets composed of all known nutrients (such as casein, glucose, gelatin, methionine, corn oil, purified salt mixture, and synthetic vitamins) except the nutrient being studied, groups of very young animals are reared in wire-floored cages under standard controlled conditions of heat, light, water, etc. The effect of dietary variation is studied by measurement of weekly weight changes, food consumption, and by clinical and biochemical changes in the animal and its tissues. Approximately 15 different groups (about 100 animals) are started on experiment each week and are continued 4 to 8 weeks.

Major Findings: This past year a variety of sub-projects were concluded or are in progress. Major findings include:

(1) The addition of relatively high levels of lactose (20%) to a synthetic diet for the chick resulted in improved growth rates. The reason for this effect is being studied.

(2) From 3 to 10% of finely ground bentonite was toxic when added to the synthetic diet of the chick. This toxicity was prevented by the injection of, or feeding of, high levels of vitamin A.

9. PROJECT DESCRIPTION - Continued

(3) The chick tolerates as much as 1% aureomycin in the diet over a 4 week period without signs of toxicity.

(4) When an amino acid mixture supplying known requirements of all amino acids is given to the chick, growth is very poor. Additional studies indicated that the chick requires an unidentified factor(s) in casein for growth.

(5) Dietary fat or fatty acids may not be required by the chick. In a number of experiments growth of chicks fed diets devoid of fat or fatty acids was equal to control chicks given fat. No requirement for dietary vitamin E was seen when the fat was removed from the diet.

(6) In studies with folic acid deficiency in the chick a number of compounds related to pteroylglutamic acid were fed and the specificity of the vitamin in overcoming a deficiency was confirmed. Ascorbic acid had a definite sparing action but had no effect in other deficiencies studied including pantothenic acid and nicotinic acid.

(7) Some evidence was found for an unidentified growth promoting factor in egg yolk and liver.

(8) A semi-synthetic diet containing all known growth factors has been developed for the mouse that results in normal growth and development when fed to 10 to 14 day old mice weighing only 6-8 grams. The diet has been found to be excellent for nutrition experiments now in progress.

Significance to NIAMD Research: The project provides basic information essential to the complete understanding of nutritional and biochemical relationships in metabolism and disease.

Proposed Course of Project: Emphasis this next year will be devoted to the importance of still unidentified factors for the chick and the mouse. Wherever possible, properties of such factors will be studied. Continued studies will be made on requirements and interrelationships of folic acid, ascorbic acid, pantothenic acid, other vitamins, fat, amino acids, and minerals. Findings obtained with one animal will be compared with other animals.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD-62113-8
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	21,300	5/6	3	3 5/6	5/6	2 2/3	3 1/2	
FY 1956	25,300	1	3	4	1	3	4	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD- 62113-8
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Briggs, G. M. Recent advances in poultry nutrition. Proc. 9th Distillers' Feed Conference, Cincinnati, Ohio, March 10, 1954, p. 64.

Briggs, G. M. Major contributor to tables 2, 3, 4, 5, 6, and 7 and contributor to tables 45 and 80 in "Standard Values in Nutrition and Metabolism" edited by E. C. Albritton, Wright Air Development Center, Technical Report 52-301, pages 7-17, 72, and 155-163, 1954.

Briggs, G. M., and F. S. Daft. Pantothenic acid (estimation, occurrence, pathology, and requirements of animals). Part of chapter for "The Vitamins" edited by Sebrell and Harris, Academic Press, 1954, pages 628-630, 633-669, and 682-687.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Biochemistry and Physiology of Nutrition
SECTION

4. Bethesda
LOCATION

5. NIAMD-62113-9
SERIAL NUMBER

6. Nutritional Studies with the Guinea Pig
PROJECT TITLE

7. Dr. Mary E. Reid
PRINCIPAL INVESTIGATOR

8. Dr. G. M. Briggs; Ligia O. Ortiz
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To determine (a) deficiency effects (gross and microscopic) of different nutrients, (b) the quantitative requirement of such nutrients, (c) to study their physiological action and interrelation with other nutrients, (d) to discover possible substitution compounds, and (e) reasons for favorable or unfavorable action of such compounds.

Methods Employed: Guinea pigs at 2 to 4 days of age, weighing approximately 100 g. were placed on a purified diet complete in all known nutritional factors except the one under investigation. To study the requirement for a nutrient the same basal diet minus the nutrient was employed; graded amounts of the nutrient were added to the diets of different groups of animals. The lowest level which gave the maximum growth was considered to be the approximate level required.

Major Findings: A. Choline studies:

(1) Choline deficiency was produced in the guinea pig for the first time. Deficiency symptoms: Retarded growth, weak muscles, reduction in number of erythrocytes, lowered hematocrit and hemoglobin values, small subcutaneous and adrenal hemorrhages but no noticeable kidney hemorrhages and no marked fatty infiltration of the liver. In a chronic type of deficiency some of the animals succumbed suddenly, apparently as a result of a circulation failure.

(2) Requirement: 1.0 to 1.5 g./kg. of diet.

9. PROJECT DESCRIPTION - Continued

(3) Substitution compounds: Neither betaine nor methionine (important in the rat) produced any benefit when added to diets lacking choline but both supplemented sub-optimal levels of choline. Dimethylaminoethanol was equal to choline. When methylaminoethanol and methionine were fed together, they were as satisfactory as a corresponding level of choline. The guinea pig apparently requires a dietary supply of both moieties of the choline molecule to cover its metabolic requirements.

B. Fat studies:

(1) Fat deficiency was produced in the guinea pig for the first time. Deficiency symptoms: Retarded growth, dermatitis, skin ulcers and loss of fur - could be overcome with corn oil or linoleic acid.

(2) Requirement: Same growth secured with fat levels of 1 to 15%; dermatitis developed on low fat levels. Hydrogenated lard (containing no unsaturated fatty acids) produced better growth than the fat-free basal diet. There is still some question as to whether the guinea pig requires only unsaturated fatty acids or fat as such, or both.

(3) Linoleic acid: When 30 mg./day were fed, growth was less than on 1% corn oil (latter supplied 100 mg. linoleic acid/day).

C. Vitamin E. studies: Severe vitamin E deficiency was produced. Its onset was hastened by omitting potassium acetate from the diet. Symptoms were severe muscular dystrophy, slight fat infiltration of livers, sudden death in a few animals.

D. Amino acids: Addition of arginine to 20% casein diet produced growth equal to that on the 30% casein diet. Glycine and methionine had no effect.

E. Salts: The Brigg's salt mixture (6% of diet) produced as good growth as any tested. Potassium acetate supplement (2.5%) is needed in purified diets.

Significance to NIAMD Research: A fuller knowledge of guinea pig nutrition is desirable because, with the exception of the monkey, this animal is in some respects more like man than any other experimental animal. Since, through our investigations, it has become possible to rear them easily on a purified diet, they can be used for

9. PROJECT DESCRIPTION - Continued

studying factors responsible for (1) abnormal mineral metabolism such as occur in certain forms of arthritis, (2) degeneration of tissues such as dystrophy of muscles as observed in choline, vitamin E and potassium deficiencies, (3) imbalances in enzyme and hormone production such as the elevated xanthine oxidase in the livers of vitamin E-deficient animals, (4) imbalances in the production of red and white blood cells by variations in dietary vitamin C, B_{12}, and folic acid, (5) the injurious effect upon the gastrointestinal tract caused by the lack of certain vitamins such as folic acid, as well as in many other problems.

Proposed Course of Project: The above studies will be extended to determine the requirement of the guinea pig for fats and essential fatty acids, for amino acids, and other nutrients. The interrelationships of vitamin C and folic acid, using the Sherman scorbutigenic diet, will be studied. It is likely that some of the accepted scurvy symptoms are probably due to a double deficiency of vitamin C and folic acid.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD-62113-9
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	18,300	1 1/3	1 1/3	2 2/3	1 1/3	1 1/3	2 2/3	
FY 1956	25,300	1	3	4	1	3	4	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

Laboratory of Pathology and Histochemistry, NIAMD- 62123-65 and NIAMD -62123-66

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD-62113-9
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Reid, M. E. Ascorbic acid. VIII. Effect of Deficiency in Animals (pp. 269-347). XI. Requirements of Animals (pp. 380-388). XII. Future Problems (pp. 391-393). Sections of Chapter 2, The Vitamins, edited by Sebrell and Harris, Academic Press, New York, 1954.

Reid, M.E., and G. M. Briggs. Nutritional Studies with the Guinea Pig. II. Pantothenic Acid. J. Nutrition 52: 507, 1954.

Reid, M. E. Nutritional Studies with the Guinea Pig. B-Vitamins other than Pantothenic Acid. Proc. Soc. Exptl. Biol. Med. 85: 547, 1954.

Reid, M. E. Production and Counteraction of a Fatty Acid Deficiency in the Guinea Pig. Proc. Soc. Exptl. Biol. Med. 86: 708, 1954.

Reid, M. E. Nutritional Studies with the Guinea Pig. III. Choline. J. Nutrition 55 (in press).

Reid, M. E. Table 89 on Ascorbic Acid in Standard Values in Nutrition and Metabolism, edited by E. C. Albritton, Wright Air Development Center, Technical Report, pp. 155-6, 1954.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None.

R.P.C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Biochemistry and Physiology of Nutrition
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62113-10
SERIAL NUMBER

6. Nutritional effects resulting from exposure of diets to ethylene oxide.
PROJECT TITLE

7. Dr. E.A. Hawk; Dr. O. Mickelson
PRINCIPAL INVESTIGATORS

3. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To determine the nutritional changes resulting from the exposure of diets to ethlene oxide and related gases.

Methods Employed: Finely ground diets are exposed to known concentrations of gas for definite periods of time. After aerating the diets to remove residual traces of the gas, the diets are fed to animals (rats, chicks). Control groups of animals are fed the unexposed diets. Where growth failure occurs various nutrients are fed to determine the factor(s) in which the treated diets is most deficient. Chemical and microbilogical analyses are made on the exposed diets to see which nutrients are destroyed.

Major Findings: Exposure of purified and stock diets to ethylene oxide diets. (The exposure time and concentration of ethylene oxide were comparable to those used in the commercial sterilization of food products.) Treatment of each component of the purified diet showed that little if any damage was done to the vitamins. Chemical and microbiological analyses indicate that all of the thiamine and most of the riboflavin are destroyed when synthetic vitamins are suspended in starch and are destroyed under similar conditions.

Preliminary studies show that enriched white flour exposed to ethylene oxide is changed nutritionally to approximately the same extent as the purified diet.

Significance to NIAMD Research: Ethylene oxide is being used on a small scale for the sterilization of a few food products. It is being used to a greater extent in the streilization of a variety of pharmaceutical products, especiall those which cannot be subjected to heat sterilization.

The changes produced by ethylene oxide on the vitamins may be of interest from a physiological standpoint. The present work suggests that growth inhibitors are formed when the vitamins are treated with ethylene oxide. It is too early to determine their potential value but one suggestion might be as possible aid in the control of obesity.

Proposed Course of Project: The mechanism involved in the ethylene oxide destruction of the vitamins will be studied and attempts will be made to determine the compounds formed as a result of ethylene oxide treatment. Studies may be extended to other foods since Camp Dietrick has proposed ethylene oxide as a major defense against any biological warfare.

R.P.C. - 2
December 1954 Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62113-10
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	17,700	1 1/3	1	2 1/3	1 1/3	1	2 1/3	
FY 1956	22,800	2	1 1/3	3 1/3	2	1 1/3	3 1/3	

12. BUDGET ACTIVITY:

RESEARCH ☒
ADMINISTRATI
ADMINISTRATION ☐

REVIEW & APPROVAL ☐
TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) ITEM 1

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO (S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62113-10
SERIAL NUMBER

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Biochemistry and Physiology of Nutirtion
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62113-11
SERIAL NUMBER

6. The nutritional requirements of the rabbit
PROJECT TITLE

7. Dr. O. Mickelsen
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To determine the nutritional requirements of the rabbit: A study of mineral interrelationships.

Methods Employed: Three-week old rabbits were fed a purified diet containing varying levels of fat and casein. The influence of sodium, potassium, and calcium supplements to the diet was studied. Weanling rats were fed a diet containing minimal amounts of sodium and/or potassium. The effect of varying the anion associated with the preceding elements was studied as far as growth was concerned.

Major Findings: The action of supplemental sodium, potassium, and calcium in increasing growth and decreasing mortality of 3-4 week old rabbits fed purified diets can be explained partially by correcting an acidic condition in the animal. However, that does not account for the entire action since there were many cases where the blood pH was low while growth was good.

When any of these elements were added as the chloride, not only was the growth promoting effect no longer apparent but the mortality of the rabbit was increased. Studies with rats receiving a purified diet containing low but adequate levels of sodium and potassium confirmed the apparent toxicity of chlorides.

Proposed Course of Project: Work has been halted pending the recruitment of a scientist to take over the project.

R.P.C. - 2
December 1954

Analysis of NIH Program Activites

Budget Data Sheet

10. NIAMD - 62113-11
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	5,700	1/3	1/3	2/3	1/3	1/3	2/3	
FY 1956	5,700	1/3	1/3	2/3	1/3	1/3	2/3	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO (S) IF WITHIN NIH)

None

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62113-11
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Wooley, Jerald G., and Olaf Mickelsen. Effect of potassium, sodium or calcium on the growth of young rabbits fed purified diets containing different levels of fat and protein. J. Nutrition 52: 591 (1954).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Biochemistry and Physiology of Nutrition
SECTION

4. Bethesda
LOCATION

5. NIAMD-62113-12
SERIAL NUMBER

6. Experimental obesity in animals
PROJECT TITLE

7. Dr. O. Mickelsen
PRINCIPAL INVESTIGATOR

8.
8. Samuel M. Takahashi
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To determine the biochemical and physiological alterations that occur in animals during the development of obesity and the subsequent loss of weight by obese animals.

Methods Employed: The rats are fed a high fat (60-63%) diet on which they attain a weight that is approximately twice that of stock controls. At termination of experiment animals are killed, organs weighed and examined for gross pathology, carcass analyzed for protein, fat, moisture, and ash. Rats reaching a weight of approximately one kg. have been put on a variety of reducing regimens. As this phase of study is completed rats will be killed and treated as above. Obese rats and normal weight controls have been exposed to simulated high altitudes in order to study the effect of this stress on the physiological response of the obese rats.

Major Findings: The percentage of fat in the body of the rat raised on a free-feeding regimen is directly related to the body weight. The fat content increases from approximately 12% for 300 g. rats to 60% for 1200 g. rats. These values are for rats that were in weight equilibrium at the time of autopsy.

There are suggestions from our earlier work that when weanling rats are put on the high fat diet they attain a higher final weight than when adult rats are started on the same diet. Controlled studies are under way which so far confirm that observation.

Reduction in body weight of obese rats was achieved by feeding restricted amounts of the high fat ration or unlimited amounts of a commercial stock diet. The weights attained at the end of the reduction regime were the same as those of normal adult rats.

9. PROJECT DESCRIPTION - Continued

Exposure of the obese rats to simulate high altitude indicated that they could not tolerate the low atmospheric pressure as well as normal weight rats (work done with Dr. Altland).

When different strains of rats are started on the high fat diet the maximum weight attained varies with the strain. At the end of 25 weeks on the high fat diet, the NIH black strain averaged 356 g., the Sprague-Dawley, 464 g., and the Osborne-Mendel, 666 g.

The pathological work done on the obese rats by Dr. Sokoloff shows degeneration of the β-cells in the anterior pituitary and osteo-arthritic lesions in the bones. The kidneys of many of the obese rats are 2 to 3 times the normal size; they show extensive hemorrhagic areas with pitted cortex and albumin plugs in the bladder. The testes and seminal vesicles are small with signs of interstitial tissue degeneration. The liver is enlarged both on an absolute and on a proportionate basis; in many cases the livers are fatty. The adrenals are slightly enlarged.

Significance to NIAMD Research: Obesity is listed as one of the major health problems today. The development of a means of producing obesity in experimental animals entirely by dietary means will permit the study of obesity in animals uncomplicated by other physiological changes. The primary emphasis of this work will be on the changes that result from a reduction in body weight.

Proposed Course of Project: Obese rats will be carried on the reducing regimen until they have attained the weight of normal adults. They will then be studied to see if their physiological and metabolic functions are the same as those in animals that were never obese. These studies will include blood pressure measurements, body composition, reproductive capacity, incidence of disease, longevity, etc.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD-62113-12
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	19,600	2/3	3 1/3	4	1/3	3 1/3	3 2/3	
FY 1956	23,600	2/3	4	4 2/3	1/3	4	4 1/3	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

Laboratory of Physical Biology, NIAMD-62129-87
Laboratory of Pathology and Histochemistry, NIAMD- 62123-69

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD-62113-12
SERIAL NUMBER

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Mickelsen, O. The addition of specific nutrients to foods. Public Health Health Reports 69: 275, 1954.

Caster, W. O., O. Mickelsen, and A. Keys. The determination of pyramin. J. Lab. and Clin. Med. 43: 469, 1954.

Taylor, H. L., A. Henschel, O. Mickelsen, and A. Keys. Some effects of acute starvation with hard work on body weight, body fluids, and metabolism. U.S.A.F. School of Aviation Medicine, Randolph Field Proj. No. 21-32-004, Report No. 5, 1954.

Caster, W. O., and O. Mickelsen. Factors influencing the yeast fermentation methods for thiamine and pyramin. J. Agr. and Food Chem. 2: 1073, 1954.

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

P.C. - 1

Analysis of NIH Program Activities

Project Description Sheet

1. NIAMD
INSTITUTE

2. Laboratory of Biochemistry and Nutrition
LABORATORY OR BRANCH

3. Biochemistry & Physiology of Nutrition
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NIAMD-62113-13
SERIAL NO.

6. Isolation of Factor 3 Against Dietary Necrotic Liver Degeneration
PROJECT TITLE

7. K. Schwarz
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: A new factor, designated Factor 3, was shown previously to prevent dietary necrotic liver degeneration. Factor 3 appears to be a new vitamin. The aim of the project is to isolate this new principle in order to identify it chemically and to make it available for clinical and nutritional studies.

Methods Employed: A fractionation procedure is worked out step by step and is constantly and successively developed further, which allows the concentration of Factor 3 from various natural source materials. Processes such as fractionated absorption and elution, chromatography, solvent extraction, and precipitation with various agents, are applied. Special, new techniques are developed, which are particularly suitable for the purification of our unidentified substance.

All fractions and also numerous other natural products and chemical substances are tested in the prophylactic animal assay for activity in preventing dietary liver necrosis. Testing operations are performed, using routinely 250 new a animals weekly. Weanling rats of the inbred Fisher strain are used.

Major Findings:

1. Screening natural source materials for Factor 3, forty different yeast samples have been tested to date. All Brewer's yeast samples are good sources;

"primary grown" yeasts and Baker's yeasts are ineffective. Various dietary materials from Guatemala are being assayed.

2. The purification process worked out for Factor 3 (12 steps) permits routine production of mg quantities of highly active material (53000 units per g). This constitutes a 26000 fold purification. Pilot Plant operations have been reorganized, increasing the output of crude Factor 3 concentrates up to twenty-five times. The laboratory process has been adjusted to the new, improved raw product, so that now larger quantities of highly purified Factor 3 become available. From such fractions, a number of crystalline by-products have been isolated.

3. A short-term assay for Factor 3 has been developed using the Warburg technique measuring oxygen consumption of liver slices after stomach tubing of Factor 3. This is used routinely now for testing Factor 3 activity within 18 hours.

Significance to NIAMD Research: Factor 3 appears to be a new vitamin. As such, it will have an important role in intermediary metabolism and probably afford new ways and means to treat diseases which hitherto were incurable, particularly fatal diseases of the liver.

Proposed Course of Project: The fractionation of highly concentrated Factor 3 fractions has to be carried out further until, finally, the substance can be obtained in sufficient quantities in crystalline form. Subsequently, its chemical identity has to be established and ways of synthesis or large-scale preparation have to be developed.

Analysis of NIH Program Activities

Budget Data Sheet

NIAMD-62113-13
SERIAL NO.

BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
Y 1955	33,800	1 2/3	4	5 2/3	1 2/3	3 2/3	5 1/3	
Y 1956	44,800	2 2/3	5	7 2/3	2 2/3	4	6 2/3	

BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

Section on Fractionation and Isolation - NIAMD-62116-28

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

C. - 3

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

NIAMD-62113-13
SERIAL NO.

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

K. Schwarz. Introduction: Liver Necrosis Versus Fatty Liver and Cirrhosis. Ann. N. Y. Acad. Sci., 57: 6, 617 (1954).

K. Schwarz. Factors Protecting Against Dietary Necrotic Liver Degeneration. Ann. N. Y. Acad. Sci., 57: 6, 878 (1954).

K. Schwarz. Nutritional Liver Diseases Up-to-Date. The Merck Report, 63: 3, (1954).

LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

P.C. - 1

Analysis of NIH Program Activities

Project Description Sheet

NIAMD
INSTITUTE

2. Laboratory of Biochemistry and Nutrition
LABORATORY OR BRANCH

Biochemistry and Physiology of Nutrition
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

NIAMD-62113 -14
SERIAL NO.

Studies on the Terminal Phase of Dietary Necrotic Liver Degeneration
PROJECT TITLE

W. Mertz - Guest
PRINCIPAL INVESTIGATOR

OTHER INVESTIGATORS

PROJECT DESCRIPTION

Objectives: A. To determine the causes and the nature of events leading to death from dietary necrotic liver degeneration in rats.

B. To assay different substances, especially vitamin E and Factor 3 as to their therapeutic properties in the terminal phase of dietary necrotic liver degeneration.

Methods Employed: Rats dying from liver necrosis were observed, respiration, heart beat, temperature, reflexes, blood glucose, appearance of the liver and of the abdominal blood vessels were studied. The response of blood glucose to intravenously and perorally injected glucose was measured in sick and normal animals. Blood glucose concentrations in the portal vein of normal and dying animals were studied.

Animals dying from necrotic liver disease were given different treatments and the effect upon survival time and physiological functions were observed.

Major Findings: The immediate causes leading to death from dietary necrotic liver degeneration are severe hypoglycemia and vascular shock. Hypoglycemia develops a few hours before death. It is due to a defect in intestinal absorption since stomach and intestines are full of diet in dying animals and since glucose disappearance from the blood is much slower than in normals. Portal blood glucose concentrations in such animals are consistently near zero, even after oral administration of glucose.

The failure of glucose absorption can be favorably influenced by intraperitoneal injection of large amounts of isotonic Na Cl solution. Glucose then appears in the blood, the symptoms of hypoglycemia disappear and the animals survive for an average of 17 hours.

Significance to NIAMD Research:

Knowledge of the nature of the terminal phase of dietary necrotic liver degeneration is important because there seems to exist a certain relationship between the symptoms of this disease and liver diseases in the human. It is hoped that new methods can be developed for the treatment of the terminal phase of human liver injuries for which, up-to-date, no reasonable ways of treatment exist.

Proposed Course of Project: The effect of vitamin E and Factor 3 on carbohydrate balance in sick animals will be studied further.

The role of vascular disturbances in the development of dietary necrotic liver degeneration will be more closely investigated, especially those of the portal system and of the circulation in the liver.

Therapeutic attempts will be continued with purified Factor 3.

.C. - 2

Analysis of NIH Program Activities

Budget Data Sheet

NIAMD-62113-14
SERIAL NO.

. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	6,600		1 1/3	1 1/3		1 1/3	1 1/3	
FY 1956	6,600		1 1/3	1 1/3		1 1/3	1 1/3	

BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

None

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

.C. - 3

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

NIAMD -62113-14
SERIAL NO.

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

PC. - 1

Analysis of NIH Program Activities

Project Description Sheet

NIAMD
INSTITUTE

2. Laboratory of Biochemistry and Nutrition
LABORATORY OR BRANCH

Biochemistry & Physiology of Nutrition
SECTION

4. --
LOCATION (IF OTHER THAN BETHESDA)

NIAMD -62113-15
SERIAL NO.

The Metabolic Lesions of Dietary Necrotic Liver Degeneration
PROJECT TITLE

S. S. Chernick
PRINCIPAL INVESTIGATORS

OTHER INVESTIGATORS

PROJECT DESCRIPTION - Metabolic Lesions in Dietary Necrotic Liver Degeneration

Objectives: The objective of this project is to determine the sequence of metabolic changes that precede and give rise to dietary necrotic liver degeneration.

Methods Employed: The metabolism of tissue, mainly of liver, of rats with dietary necrotic liver degeneration is assessed by means of Warburg respirometer studies on slices, homogenates or subcellular components under conditions designed to measure the intactness of various enzyme systems. Appropriate chemical procedures (coenzyme determinations, etc.) are employed to extend these observations to specific enzymes.

Major Findings: In contrast to the stable in vitro respiration of normal liver, oxygen consumption of livers from rats fed the necrogenic diet decline after a short period of incubation. Only liver shows this respiratory lesion. The change in metabolism is observed long before any histological manifestation of the disease appears. It is readily reversed by the short-term administration to the animal of vitamin E or Factor 3. Homogenates of deficient livers, fortified with adenine nucleotides (DPN and ATP) respire in the normal fashion. Coenzyme concentration studies have not provided clues as to the site of the lesion. Coenzyme A, while low in deficient livers, does not correlate with necrosis or respiratory decline.

D-62113-15
AL NO.

Significance to NIAMD Research: Almost nothing is now known of the sequence of biochemical events leading to cellular death in liver diseases. These studies delineating metabolic changes may reveal the weak point in cellular metabolism and suggest therapeutic procedures. Further, since dietary necrotic liver degeneration is prevented by vitamin E, cystine or Factor 3, an opportunity is offered to study the participation of these substances in liver metabolism.

Proposed Course of Project: The finding that metabolism is defective in the slice but normal in the homogenate suggests that the procedures employed in maintaining the concentration of adenine nucleotides may be involved. During the next year we shall concentrate on these poorly understood mechanisms. A study of oxidative phosphorylation by mitochondria prepared from deficient and protected livers has been initiated. The studies on the participation and localization of vitamin E and Factor 3 in cellular metabolism will continue.

C. - 2

Analysis of NIH Program Activities

Budget Data Sheet

NIAMD-62113-15
SERIAL NO.

BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	16,700	2	1	3	1 1/3	1	21/3	
FY 1956	17,700	2	1	3	1 1/3	1	2 1/3	

BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

.C. - 3

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

NIAMD-62113-15
SERIAL NO.

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

7. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Endocrinology
SECTION

3. Locaesda
LOCATION

5. NIAMD - 62114-16
SERIAL NUMBER

6. The influence of the central nervous system on metabolism
PROJECT TITLE

7. Dr. Kathryn Knowlton . Dr. Evelyn Anderson
PRINCIPAL INVESTIGATORS

3. Mrs. Beatrice S. Miles (Guest-Walter Reed)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: To study the influence of the central nervous system on metabolism using dogs with neurosurgical lesions.

Methods Employed: Dogs are used for this study. Using aseptic operative technique transections are made at the midbrain level and at various levels of the spinal cord. The animals are maintained at a constant intake before and after operation. Determinations of nitrogen, sodium, and potassium balances, glucose tolerance and insulin sensitivity are made. The study is carried on for 3 weeks before operation and as long as the animal survives postoperatively, which varies from one week up to several months.

Major Findings: Following transection at the midbrain level all of the dogs showed a decreased glucose tolerance, a urinary retention of sodium, and increased urinary excretion of potassium, and a marked creatinuris. These changes lasted for a period of 1 to 4 weeks, except for the sodium retention, which disappeared after one week. The creatinine excretion usually fell 25 to 50 percent on the day of operation and remained at that low level. In some of the animals there was a negative nitrogen balance which lasted about 3 weeks. The fasting blood levels of creatinine, nonprotein nitrogen, sodium and potassium remained consistently normal throughout the postoperative period. The stress of operation and the disturbed hormone pattern were not associated with any increased adrenal hormone in the urine.

Transection of the spinal cord between C.6 and T.3 was followed by a negative nitrogen balance, creatinuria, sodium retention, and increased excretion of potassium. These changes persisted for about 3 weeks postoperatively. The creatinine excretion remained at the normal level for about 2 weeks post-operatively and then gradually decreased as muscle wasting in the lower trunk and extremities became apparent. The glucose tolerance was significantly increased. Adrenal hormone excretion in the urine was increased only on the day of the transections; otherwise it remained at the normal level. It was not increased following severely stressful surgery, such as laparatomy without anesthetic, or hemidecortication.

Significance to NIMD research: This is fundamental research underlying the problem of psychosomatic medicine and many other problems of clinical medicine. This is the first study reported in medical literature as far as can be determined.

Proposed Course of Project: This project is being amplified by three new projects:

(1) The influence of the central nervous system on creatine and creatinine metabolism as based on transections of midbrain and spinal cord in dogs.

(2) The influence of the central nervous system on endocrine activity, and specifically on the adrenal cortex and medulla.

(3) The influence of the central nervous system on cardiovascular renal function.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIMD 62114-16
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	14,700	1	1	2	1	1	2	
FY 1956	14,700	1	1	2	1	1	2	

12. BUDGET ACTIVITY:

RESEARCH ☒
ADMINISTRATION ☐
REVIEW & APPROVAL ☐
TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

Division of Neuropsychiatry, Army Medical Service Graduate School
Walter Reed Medical Center
Armed Forces Institute of Pathology

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIMD - 62114-16
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

The Influence of the Central Nervous System on Metabolism and Endocrine Activity as Based on Transections of the Brain Stem in Dogs.
Evelyn Anderson, Kathryn Knowlton, William T. Spence, S.M. McCann,
Gert L. Laqueur, David McK. Rioch, and Webb Haymaker.
(Accepted for publication by Acta Neurovegetativa, Vienna.)

Disorders of the Hypothalamus and the Pituitary Gland - Chap. 21 -
E. Anderson and W. Haymaker   Clinical Neurology. Ed. by A.B. Baker.,
New York, Hoeber, 1955

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Endocrinology
SECTION

4. Bethesda
LOCATION

5. NIAMD-62115-17
SERIAL NUMBER

6. Studies on the physiology of ACTH and hypothalamus
PROJECT TITLE

7. Dr. Robert Bahn
PRINCIPAL INVESTIGATOR

8. Dr. Gert L. Laqueur; Dr. Jacob Furth (Guest-Harvard); Dr. Raul Echenique Gonzales (Guest-Univ. of Havana)

9. PROJECT DESCRIPTION

Objectives: The objective of this project is to further investigate the physiology of ACTH with respect to the neurohumoral factors governing ACTH secretion and the effects of prolonged ACTH stimulation upon the organism.

Methods Employed: Transplantable ACTH-producing tumors have been used as a source of endogenous ACTH in LAF-1 mice. The course of development of tumor-induced hyperadrenal corticism has been followed by studies of water, sodium, potassium, nitrogen balances, urinary creatine and creatinine excretion, blood glucose, circulating leucocytes, and estrus cycling.

Major Findings: By the methods described hyperadrenal corticism may be produced in the mouse. This is characterized by hypertrophy of the a adrenal glands, obesity, susceptibility to infection, profound lymphopenia, interruption of estrus cycling, marked increase in water turnover, moderate increase in the excretion of sodium, potassium, nitrogen, creatine and creatinine.

Significance to NIAMD Research: Previously only ACTH derived from other species could be administered to mice to produce hyperfunctioning adrenal cortices. The interpretation of the results of such studies were necessarily complicated by questions of species differences and the possible development of immune antibodies. The availability of the ACTH-producing tumor-bearing mouse has now made it possible to study the effects of continuous endogenous ACTH stimulation under laboratory conditions without the complication of antihormone formation.

The accessibility of the tumor for local injection, removal, biopsy, transplantation should provide greater experimental flexibility than is provided by the normal pituitary gland which is located within the skull.

The results of these studies may add to the understanding of Cushing's Disease which is the human counterpart to experimental hyperadrenal corticism.

Proposed Course of Project: Investigation of neurohumoral secretory mechanisms will include studies of the effects of intratumor implantation of known chemical mediators of ACTH secretion upon adrenal cortical function. The relationship of the central nervous system to pituitary secretion will be investigated in mice-vearing tumors in the region of the hypothalamus, etc. Also planned is a study of the effects of varying durations of endogenous ACTH stimulation upon the histology and chemical composition of the adrenal glands.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62115-17
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	7700	1		1	2/3		2/3	
FY 1956	8900	1		1	1		1	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62115-17
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Neurosecretory Pathways between the Hypothalamic Paraventricular Nucleus and the Neurohypophysis. G.L. Laqueur - J. Comp. Neurology 101: 1-12, 1954.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Endocrinology
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62114-18
SERIAL NUMBER

6. Isolation, chemistry and bioassay of anterior pituitary hormones
PROJECT TITLE

7. Dr. Robert W. Bates, Dr. Peter Condliffe
PRINCIPAL INVESTIGATORS

8. Mr. Tulane Howard, Miss Alice Laskey, Dr. Jacob Furth (Guest-Harvard University)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To isolate the anterior pituitary hormones (thyrotrophin, ACTH, growth hormone, gonadotrophins, and prolactin) and to determine their chemical composition. To compare purified hormones isolated from pituitary glands with those isolated from transplantable mouse pituitary tumors.

Methods Employed: Extraces are made of pituitary glands and of mouse pituitary tumors. These extracts are fractionated and studied by salt fractionation, solvent fractionation, isoelectric precipitation, preparative electrophoresis, chromatography and countercurrent distribution. Identification and quantitative estimation of the amino acid constitution of purified fractions are made by paper chromatography after hydrolysis with or without formation of suitable derivatives. The potency of all fractions must be determined by bioassay using iodine depletion in the chick thyroid for thyrotrophin; bioassay using iodine depletion of the adrenal of the rat for adrenocorticotrophin; corpsac weight increase in pigeons for prolactin; seminal vasicle weight increase in rat for luteinizing hormone; uterine and ovarian weight increase in rat for follicle stimulating hormone and body weight increase in the rat for growth hormone.

Major Findings: The thyrotrophic hormone has been studied chiefly to date. A reliable method has been evolved for the bioassay of thyrotrophin using the one day old chick. It has been found that fasting of the animals during the entire period of the test and also the presence of a high level of iodine in the thyroid are necessary conditions for a satisfactory assay.

Preliminary results on fractionation of thyrotrophin have been obtained. Mouse pituitary tumors were found to contain approximately five times as much thyrotrophin per unit weight as the pituitary glands of sheep, cattle, or hogs.

There is some evidence that a method for bioassay of adrenocorticotrophin using normal rats instead of hypophysectomized rats may prove reliable.

Significance to NIAID Research: The mechanism of action of the pituitary hormones is not, as yet, understood. Progress in this field depends upon an increased understanding of the chemistry of the hormones. To accopmlish this end, it is necessary to isolate in a chemically pure state and to characterize these hormones. It is known that the pituitary secretes six hormones and it is important to determine whether others also exist.

Proposed course of project: The rate of progress in the isolation of the hormones is directly related to the availability of satisfactory methods of bioassay. Considerable effort must be continuously expended to maintain and develop more accurate, sevsitive, rapid and specific methods of bioassay. The methods of identifying amino acid constitution developed in studies on the structure of insulin and subsequently applied to studies on oxytocin, vasopressin and adrenocorticotrophin will be applied to thyrotrophin and growth hormone. Search for additional pituitary hormones will be maintained

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62114-18
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	30,700	2 3/3	1	3 2/3	2 2/3	1	3 2/3	
FY 1956	30,700	2 2/3	1	3 2/3	2 2/3	1	3 2/3	

12. BUDGET ACTIVITY:

RESEARCH ☐
ADMINISTRATION ☐
REVIEW & APPROVAL ☐
TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARRALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62114-18
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. -1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Endocrinology
SECTION

4. Bethesda
LOCATION

5. NIAMD-62114-19
SERIAL NUMBER

6. Assay of Insulin in Blood.
PROJECT TITLE

7. Dr. Evelyn Anderson; Dr. Robert Bates
PRINCIPAL INVESTIGATORS

8. Mrs. Frances W. Franco; Robert Gray (Guest)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objective of this project is to devise a method for the assay of minute amounts of insulin which would be applicable for the assay of insulin in blood.

Methods Employed: The alloxan diabetic hypophysectomized mouse is used. The fall in blood sugar in response to an intravenous injection of insulin is used as the measurement of response. The technical difficulties of collecting blood samples in the presence of vasoconstriction due to an intravenous injection of serum, and of determining blood sugar using amounts of blood as low as 0.01 ml. are some of the problems which arise in developing a successful assay method.

Major Findings: Amounts of insulin as low as 100 microunits can be detected. (1 microunit is one millionth of a unit or 3.6×10^{-8} mg. insulin.) Considerable gains have been made in an effort to bring the lambda value for the assay into a satisfactory range, but more work is still needed.

Significance to NIAMD Research: A satisfactory method for the assay of insulin in blood would prove a useful tool in the study of problems in carbohydrate metabolism and in diabetes.

Proposed Course of Project: To take steps to increase the sensitivity and accuracy of the method and to apply the final method to the assay of insulin in the blood of patients.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD-62114-19
SERIAL NUMBER

11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	17,300	5/6	1½	2 1/3	5/6	1½	2 1/3	
FY 1956	17,300	5/6	1½	2 1/3	5/6	1½	2 1/3	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

Office of Biometry, NIAMD-

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD-62114-19
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Endocrinology
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62114-20
SERIAL NUMBER

6. The influence of the central nervous system on creatine and creatinine metabolism as based on transections of midbrain and spinal cord in dogs.
PROJECT TITLE

7. Dr. Kathryn Knowlton
PRINCIPAL INVESTIGATOR

8. Mr. Leonard H. Kedda
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To study the role of the central nervous system in creatine and creatinine metabolism and the mechanisms by which its effects are produced.

Methods Employed: Dogs are used for this study. Using aseptic operative technique transections are made at the midbrain level and at various levels of the spinal cord. The animals are maintained at a constant food intake before and after operation. Determination of creatine and creatinine in urines of dogs subjected to transection of the central nervous system at midbrain and various cord levels. Analysis of urinary constituents for N^{15} content after administration to such dogs of glycine and creatine labeled with N^{15}.

Major Findings: Immediately after midbrain transection, creatinine excretion usually dropped permanently, while a creatinuria of unrelated magnitude was seen for a limited time only. After cervical cord transection there was a similar creatinuria. Creatinine excretion did not change immediately, but gradually declined later to a stable lower level.

Significance to NIAMD Research: Since creatine phosphate occupies a place of some importance in intracellular energy interchanges of the mammalian body, and since several hormones (e. g. androgens, estrogens, adrenocortical steroids with their

9. PROJECT DESCRIPTION - Continued

pituitary colleagues) are known to affect creatine-creatinine economy, further knowledge of factors and mechanisms of the systems involved will contribute basically to our understanding of metabolic disorders.

Proposed Course of Project: The excretion of N^{15} in urinary creatine and creatinine after feeding glycine labeled with N^{15} will be followed in dogs subjected to midbrain transection to permit more complete interpretation of the effects of midbrain damage on the metabolic course of these substances. Also, from the N^{15} content of other urinary nitrogenous constituents, information should be gained regarding other factors in the effect of the central nervous system on nitrogen metabolism.

Creatine labeled with N^{15} in the glycine moiety will be synthesized and fed, in order to label body creatine before spinal cord transection. Determination of the N^{15} content of urinary creatine and creatinine in such animals should result in direct knowledge of the source of the creatinuria following cord transection. Abundance of N^{15} in muscle creatine and creatinine will also be determined.

It is also anticipated that later studies of the modification of creatine metabolism by hormone administration or withdrawal will be of value.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62114-20
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	15,400	½	2½	3	½	2½	3	
FY 1956	15,400	½	2 1/3	3	½	2½	3	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

Section on Intermediary Metabolism, NIAMD - 62114-16

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

None

.P.C. -3
ecember 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

5. NIAMD - 62114-20
SERIAL NUMBER

6. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

See project: Influence of the CNS on Metabolism, NIAMD-62114-16.

7. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Endocrinology
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62114-21
SERIAL NUMBER

6. The influence of the Central Nervous System on Cardiovascular-renal Function
PROJECT TITLE

7. Dr. Edward W. Hawthorne (Guest- Howard University)
PRINCIPAL INVESTIGATOR

8. Mr. Harold Hall (Guest - Howard University), Dr. David McK. Rioch (Guest - Walter Reed), Dr. William T. Spence (Guest - Georgetown University), and Dr. Francis Enomoto (Guest - Georgetown University)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To study the cardiovascular-renal functional alterations incident to midbrain and spinal cord transection with the following major views in mind:

(1) To gain insight into the acute and chronic effects of loss of discreet neural influences (cortical, hypothalamic, and spinal) of cardiac and renal function.
(2) To understnad the relationship between renal electrolyte, and water excretion and the general fluid and electrolyte balance in dogs following midbrain and spinal cord transections.

Methods: Dogs are used and observations made during a control, operative, and post-operative period. The dogs are maintained on a rigidly controlled diet and daily "intake-output" records are kept. Throughout each period determinations are made of arterial pressure, renal clearances, cardiac output, measurements of various fluid "spaces" and balance studies such as nitrogen, sodium, water, and creatinine balance. Following a suitable control period each dog is subjected either to midbrain or spinal cord transection. Studies are continued during the post-operative period for a long as is deemed feasible. After this period a complete autopsy is performed with special attention being directed to the neuropathology.

Major Findings: Our studies thus far are preliminary in character and do not permit final interpretation. There was profound reduction in renal clearnace of para-ammohippurate and of creatinine during the acute post-operative period. Successive studies following midbrain transection showed no chronic reduction of renal clearances,

but rather a gradual return to the normal renal plasma flow and glomerular filtration rate. Only one dog has been completed to date. In this god midbrain transection had no effect on mean arterial pressure.

Significance to NIAMD Research: The prolonged survival of dogs with midbrain and cervical cord transections affords one an unusual opportunity to study the role of the central nervous system in the regulation of renal and cardiac function. Exactly what part the nervous system plays in the regulation of normal fluid balance, cardiac output, arterial pressure and general renal function is not know at the present time. These studies bear directly on our desire to understand clearly the mechanism of pathophysiologic alterations in the above parameters occurring in patients with specific nervous, endocrine, cardiac and renal dysfunction.

Proposed Course of project: It is inteneded to study a series of dogs with midbrain and spinal cord transection, the acute and chronic alterations in renal and cardiac function, along with changes in the fluid and electrolyte balance. Specifically we plan to study changes in the renal clearance of sodium, glomerular filtration, renal plasma flow, cardiac output, arterial pressure, extracellular fluid space and blood volume, along with balance studies including nitrogen, fluid and electrolyte balances.

R.P.C. 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62114-21

11. BUDGET DATA:

	ESTIMATED ESPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	3,000	-	-	-	-	-	-	-
FY 1956	3,000	-	-	-	-	-	-	-

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATION UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

AMSGS, Army Medical Center.
Howard University School of Medicine.
Georgetown University School of Medicine.
Armed Forces Institute of Pathology.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARRALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACIEETIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

Analysis of NIH Program Acitivties

Honors, Awards, and Publications Sheet

15. NIAMD - 62114-21
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Endocrinology
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62114-22
SERIAL NUMBER

6. The influence of the central nervous system on endocrine activity
PROJECT TITLE

7. Dr. Hildegard Wilson (Guest - Georgetown)
PRINCIPAL INVESTIGATOR

8. Dr. David McK. Rioch (Guest - Walter Reed), Dr. William T. Spence (Guest-Georgetown), , Dr. Ouay Ketusinh (Guest- FOA-fellow, Bangkok, Siam), Mr. John Borris(Guest - Walter Reed), Miss Mary G. Marques (Guest - Howard University)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The influence of the central nervous system on endocrine activity, as based on transections of the midbrain and spinal cord.

Objectives: To develop methods adequate for the routine determinations of adrenal cortical steroids and adrenal medullary hormones in the blood and urine of dogs. To apply these methods in serial analyses before and after transections of the midbrain and spinal cord.

Methods Employed: For the adrenal steroids in blood plasma, a 60% ethanolic extract is prepared which contains both free and conjugated steroids. These are then separated, the conjugates hydrolyzed, and assays performed on the combined free fractions. The corticosteroid assay involves a micro determination of 17-ketosteroids after oxidation with chromic acid, and determines both 17-hydroxy corticosteroids and 17-ketosteroids. Procedures for steroid determinations on god urine are now under study. Adrenalin and nor-adrenalin will be extracted from urine by the method of Goldenberg et al., separated by paper chromatography, and determined separately. Bioassays are being set up, and chemical assays are planned.

Major Findings: The results obtained since July 1, 1954, concern the state of

adrenal steroids in blood plasma. In human plasma about half has been found in the free state, about one fifth conjugated as glucuronides, and the remainder as acid hydrolyzable conjugates. In dog serum the totals were lower, and there was a smaller proportion of free steroids.

Significance to NIAMD Research: The evaluation of adrenal cortical function in dogs (or humans) by means of steroid assays, when only small alterations are expected, requires refined methods. It is hoped that our procedures will reveal variations in plasma levels following CNS operations, thus reflecting the effects on adrenal cortical function. Parallel analyses of adrenalin and noradrenalin should reflect the participation of the adrenal medullary hormones.

Proposed Course of the Project: It is planned to follow the total plasma steroid levels in dogs before and after transections of the midbrain and spinal cord. If alterations are found, it will be possible to extract larger volumes of plasma and determine which fraction has been affected. Chromatographic analyses of adrenal verous blood of both normal and operated dogs are also planned, in a further effort to detect alterations in adrenal cortical activity.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62114-22
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	3,000	-	-	-	-	-	-	-
FY 1956	3,000	-	-	-	-	-	-	-

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

Walter Reed
Georgetown University
Howard University
Foreign Operations Administration (fellow)

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARRALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62114-22
SERIAL NUMBER

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Enzymes and Cellular Biochemistry
SECTION

4. Bethesda
LOCATION

5. NIAMD-62115-23
SERIAL NUMBER

6. The enzymatic transformation of carbohydrates and their intermediary metabolism
PROJECT TITLE

7. Dr. B. L. Horecker
PRINCIPAL INVESTIGATOR

8. Miss P. Z. Smyrniotis
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To provide further information on the new pathway of carbohydrate metabolism in order to define the role of these reactions and intermediates in the chemistry of the cell.

Methods Employed: With enzymes purified from suitable sources the individual reactions are studied in detail and reaction products isolat and identified. These products are then employed as substrates for succeeding steps.

Major Findings: The tetrose ester formed from sedoheptulose 7-phosphate in the transaldolase reaction has been identified as D-erythrose 4-phosphate. This is the first tetrose implicated in carbohydrate metabolism. This ester participates in two further reactions, the products of which have been identified as sedoheptulose diphosphate and fructose 6-phosphate. Sedoheptulose diphosphate is a new ester whose main function appears to be to act as a reservoir for the very unstable erythrose ester.

Further studies with purified transketolase from spinach have established that this enzyme will react with D-xylulose 5-phosphate as well as with ribulose 5-phosphate. The xylulose ester was obtained for the first time by means of a purified kinase from Lactobacillus pentosus.

An identical series of reactions involving transketolase and transaldolase has been shown to account for pentose phosphate synthesis

9. PROJECT DESCRIPTION - Continued

in animal tissues and in plants. In the former pentose phosphate is used for nucleic acid synthesis, while in the latter it provides the primary CO_2 acceptor in photosynthesis. A purified kinase form spinach forms ribulose diphosphate from ribose phosphate and ATP. Ribulose diphosphate is the substrate for the carboxylation reaction in which 2 moles of phosphoglyceric acid are produced.

Two new enzyme reactions involving imidazole acetol phosphate have been found to participate in the biosynthesis of histidine. One of these represents a new type of transamination reaction in which the carboxyl group is replaced by a phosphate ester linkage. Like other transamination reactions, it requires pyridoxal phosphate.

Significance to NIAMD Research: The existence of a mechanism for the conversion of hexose monophosphate to pentose phosphate which is common to green plants and animals suggests that these reactions are important in the basic economy of the cell. Knowledge of these reactions opens the way to an examination of their status in normal and diseased cells.

Proposed Course of Project: Further work is needed to determine the detailed mechanism of the transketolase and transaldolase reactions. In particular the role of thiamine pyrophosphate in the former reaction and the participation of cofactors in the second reaction will be investigated. Further reactions involving the new esters erythrose phosphate, sedoheptulose diphosphate and ribulose diphosphate will be sought. The new kinase and carboxylating enzymes will be purified in order to determine the cofactors and reaction mechanism.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD-62115-23
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	28,500	2	2	4	2	2	4	
FY 1956	34,000	3	2	5	3	2	5	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

B. Ames - Postdoctoral Fellow of the Public Health Service, Jan-Sep 1954
Assistant Scientist Reserve, USPHS, Sep-Dec 1954
A. Weissbach - Postdoctoral Fellow, National Foundation for Infantile Paralysis
J. Hurwitz - Postdoctoral Fellow, American Cancer Society
P. Stumpf - Postdoctoral Fellow, USPHS
H. Hiatt, NIAMD- 62131-104
P. Marks, NIAMD- "

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

Section on Entermediary Metabolism NIAMD - 62117-37

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD-62115-23
SERIAL NUMBER

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

The Mechanism of Pentose Phosphate Conversion to Hexose Monophosphate by B. L. Horecker, Martin Gibbs, Hans Klenow, and P. Z. Smyrniotis. J.B.C. 207, No. 1, 393 (1954)

The Mechanism of Pentose Phosphate Conversion to Hexose Monpphosphate. II. With Pea Leaf and Pea Root Preparations. By Martin Gibbs and B. L. Horecker. J.B.C. 208, No. 2, 813 (1954).

Pentose Phosphate and CO_2 Fixation with Spinach Extracts. By A. Weissbach, P. Z. Smyrniotis and B. L. Horecker. J.A.C.S., 76, 3611 (1954).

Discussion in Symposium. By B. L. Horecker, Federation Proc., 13, No. 3, 711 (1954).

The Enzymatic Formation of Ribulose Diphosphate. By A. Weissbach, P. Z. Smyrniotis and B. L. Horecker. J.A.C.S., 76, 5572 (1954).

Tetrose Phosphate and Sedoheptulose Diphosphate Formation. By B. L. Horecker, P. Z. Smyrniotis, H. Hiatt and P. Marks. J. Biol. Chem., in press.

Purification and Properties of Yeast Transaldolase. By B. L. Horecker and P. Z. Smyrniotis. J. Biol. Chem., in press.

Carbohydrate Metabolism. By B. L. Horecker and Alan H. Mehler. Book: Annual Review of Biochemistry (1954), in press.

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Hillebrand Award (1954), Washington Academy of Sciences - Dr. B. L. Horecker

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December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Enzymes and Cellular Biochemistry
SECTION

4. Bethesda
LOCATION

5. NIAMD-62115-24
SERIAL NUMBER

6. Studies on the structure and intermediary metabolism of nucleic acids and nucleotides
PROJECT TITLE

7. Dr. Leon A. Heppel
PRINCIPAL INVESTIGATOR

8. Russell J. Hilmoe
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objective of this project is to discover pathways for the biosynthesis and breakdown of nucleic acids and smaller nucleotide units.

Methods Employed: With enzymes purified from suitable sources various biosynthetic and degradative reactions are carried out. The products are studied by means of paper chromatography, paper electrophoresis, chemical analysis and ion exchange column chromatography.

Major Findings: The first successful enzymatic synthesis of dinucleotides and larger ribopolynucleotides from small molecules such as cyclic mononucleotides, was demonstrated by us last year. Pancreatic ribonuclease and a spleen diesterase catalyzed the synthesis by an exchange mechanism. This work has been extended and other diesterases with different specificities have also been shown to possess synthetic ability.

Ribonuclease has now been purified from spleen and liver and shown to have exactly the same enzymatic properties as the pancreatic enzyme. Spleen phosphodiesterase has been further purified and characterized.

A new series of transphosphorylation reactions have been discovered. Two enzymes have been separated. One catalyzes a transphosphorylation between ATP and various nucleoside monophosphates. The other catalyzes a similar reaction between AMP and various

9. PROJECT DESCRIPTION - Continued

nucleoside triphosphates. These reactions make possible the synthesis of all the various triphosphates which are believed to be precursors in nucleic acid synthesis.

A new deaminase has been purified several hundred-fold from spleen which rapidly converts adenosine to inosine.

Significance to NIAMD Research: It is expected that these studies will provide information on the mechanisms of nucleotide and nucleic acid synthesis. These substances are basic to the economy of all cells, and their normal metabolic pathway must be understood before possible alterations in disease states can be investigated.

Proposed Course of Project: The role of cyclic nucleotides and other nucleotides in nucleic acid biosynthesis will be further investigated. Purification studies of nucleases and diesterases will be continued and their mechanism of action studied by use of O^{18} and other methods. Transphorylation reactions will be studied in greater detail, as well as a new phosphatase discovered in the course of this work.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD-62115-24
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	24,200	2	2	4	2	1½	3½	
FY 1956	27,200	2	3	5	2	2	4	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

Studies by Dr. Mary E. Maver (NCI) on another spleen nuclease are complementary to one part of the above project. NCI-

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD-62115-24
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

The action of some nucleases on simple esters of monoribonucleotides. D. M. Brown, L. A. Heppel and R. J. Hilmoe. J. Chem. Society p. 40, 1954

Nucleotides and Nucleosides. L. A. Heppel. Chapter in Chemical Pathways of Metabolism, Vol. 2, Editor D. M. Greenberg

Transphosphorylation between Nucleoside Monophosphates and Nucleoside Triphosphates. J. L. Strominger, L. A. Heppel and E. S. Maxwell. Arch. Biochem. Biophys., 52, 488, 1954

A note on the structure of triphosphopyridine nucleotide. L. A. Heppel, P. R. Whitfeld and R. Markham. J. of the Chem. Society (British). In press

Nucleotide exchange reactions catalyzed by ribonuclease and spleen phosphodiesterase. I. Synthesis and Interconversion simple Esters of Ribomononucleotides. L. A. Heppel and P. R. Whitfeld. J. of the Chem. Society (British). In press

The Enzymatic hydrolysis of ribonucleoside-2':3'-monohydrogen phosphates. P. R. Whitfeld, L. A. Heppel and R. Markham. J. of the Chem. Society (British) In press

Nucleotide exchange reactions catalyzed by ribonuclease and spleen phospho diesterase. II. Synthesis of of Polynucleotides. L. A. Heppel, P. R. Whitfeld and R. Markham. J. of the Chem. Society (British) In press

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

C. - 1

Analysis of NIH Program Activities

Project Description Sheet

NIAMD
ISTITUTE

2. Biochemistry and Nutrition
LABORATORY OR BRANCH

hzymes & Cellular Biochemistry
CTION

4.
LOCATION (IF OTHER THAN BETHESDA)

IAMD-62115-25
RIAL NO.

Sudies on the Biosynthesis and Degradation of Purines
ROJECT TITLE

sse C. Rabinowitz
RINCIPAL INVESTIGATOR

W E. Pricer, Jr.
THER INVESTIGATORS

ROJECT DESCRIPTION:

jectives: The objective of this project is to determine biological mechanisms for the degradation and synthesis of purines.

thods Employed: With enzyme preparations from animal and microbial sources, products of purine metabolism are isolated and identified using column and paper chromatography, paper electrophoresis, and chemical synthesis. The compounds accumulated by a Neurospora mutant blocked in purine biosynthesis are also investigated and the nutritional requirements of these mutants studied in growth experiments.

jor Findings: The major findings of this project during the past year have included the purification of two enzymes which has made possible, (1) the characterization of 4-aminoimidazole and formiminoglycine as intermediates in the degradation of xanthine; (2) the isolation of a nucleotide not identica with any known compound from extracts of the adenineless Neurospora mutant, and (3) the observation that this mutant organism can also grow on hypoxanthine in place of adenine only if histidine is added to the medium.

gnificance to Arthritis and Metabolic Disease Research: Purines are synthesized and are degraded to uric acid and other products by living organisms; they

D-62115-25
AL NO.

are involved in energy transfer reactions in the form of nucleotides; they are components of nucleic acids and are found in all living cells. The metabolism of purines is therefore of fundamental importance in all living organisms. Knowledge of the enzymatic reactions involved in their biosynthesis, however, is fragmentary. The metabolism of purines in microbial systems and the identification of the compounds involved has been a fruitful means of disclosing metabolic pathways and organic compounds previously unknown. The occurrence of similar pathways or compounds in other normal and diseased organisms should thus be greatly facilitated.

Proposed course of project: Problems which shall be investigated during the next calendar year include (1) the identification of the compounds and enzymatic reactions involved in the conversion of formiminoglycine to formic acid and glycine; (2) the characterization of the nucleotide accumulated by the *Neurospora* mutant; and (3) and evaluation of the general occurrence and significance in other biological systems of the compounds which have been in these studies.

Analysis of NIH Program Activities

Budget Data Sheet

IAMD-62115-25
ERIAL NO.

UDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
1955	18,800	2	1	3	2	1	3	
1956	18,800	2	1	3	2	1	3	

UDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

DENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANI-
ATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER
955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

None

F THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE
N THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR
UNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

one

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

NIAMD-62115-25
SERIAL NO.

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

Analysis of NIH Program Activities

Project Description Sheet

NIAMD
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY OR BRANCH

Enzymes & Cellular Biochemistry
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

NIAMD-62115-26
SERIAL NO.

Metabolism and Biological Function of Uridine Nucleotides
PROJECT TITLE

H. M. Kalckar (Visiting Scientist)
PRINCIPAL INVESTIGATOR

E. Maxwell
OTHER INVESTIGATORS

PROJECT DESCRIPTION:

Objectives: To follow the biosynthetic pathways by which active uridine nucleotides, involved in glucose, galactose and glucuronic acid metabolism in the liver are formed. To study the function of this type of nucleotide for the formation of coupled glucuronides (phenol, steroids) and mucopolysaccharides. In related studies to examine the metabolism of uridine diphospho glycosyl compounds in muscle and in various microorganisms.

Methods Employed: Large scale isolation of uridine diphospho glucose from yeast with the help and facilities provided by Dr. Keresztesy and the equipment available in the Section of Isolation and Fractionation. Column chromatography (Dowex-2 chloride), paper chromatography and extensive use of enzymatic ultraviolet spectrophotometric methods to study the course of reactions.

Major Findings: Drs. J. Strominger, E. Maxwell and I initiated during early September 1954 the studies on the biosynthesis of the so-called 'active' glucuronic acid through collaboration with Dr. Julius Axelrod, Laboratory of Chemical Pharmacology, National Heart Institute. The major finding of the project dealing with glucuronic acid metabolism was the observation and subsequent isolation of the hitherto unknown metabolic enzyme, uridine diphospho glucose dehydrogenase (UDPG dehydrogenase) which in the presence of diphospho pyridine nucleotide (DPN) catalyzes the oxidation of UDPG to uridine diphospho

glucuronic acid (UDPGA). The latter substance has recently been recognized as being identical with the so-called 'active' glucuronic acid. We have lately in collaboration with Dr. K. Isselbacher of NIAMD, succeeded in demonstrating that the enzymatic oxidation product of UDPG incubated with DPN and the above mentioned enzyme gave rise to a substance which proved to be UDPGA ('active' glucuronic acid) chemically as well as biologically. The isolated oxidation product in the presence of microsomes and various glucuronide acceptors such as phenols of tetrahydro cortisone (cf. Dr. Isselbacher's report) brought about a rapid and efficient formation of glucuronides of the latter compounds.

A research project dealing with the UDPG metabolism in microorganisms resulted in the observation that *Hemophilus influenzae* and *para influenzae* contain enzymes which catalyzes a degradation of UDPG quite different from that observed in mammalian tissues, yeast, *E. coli* and in nonpathogenic strains of *Hemophilus*. This project was greatly assisted by the help and experience of Dr. M. Pittman of the National Microbiological Institute. Valuable material was also kindly sent to us from Lederle Laboratories, American Cyanamide.

The project on metabolism of uridine nucleotides in muscle was performed in collaboration with Dr. W. W. Kielley of the National Heart Institute. It was found that an enzyme of the contractile protein, myosin, catalyzes the dephosphorylation of uridine triphosphate (UDP) with a rate considerably higher than that of adenosine triphosphate (ATP) (cf. Dr. Kielley's report).

ignificance to Research in Arthritis and Metabolic Diseases: The general biological importance of the uridine diphospho glycosyl compounds for the metabolism during growth (normal or pathological) and especially for the formation of the so-called mucopolysaccharides (hyaluronic acid, cartilage, bacterial immune polysaccharides) is now increasingly recognized. The discovery of the UDPG-dehydrogenase closes the missing link in the scheme describing the conversion of glucose or glycogen to glucuronides. The fact that a niacin nucleotide (DPN) is involved in the formation of active glucuronic acid poses several questions of nutritional significance. It is rather likely that diseases in which the mucopolysaccharides show pathological alterations are in a more or less direct way correlated with disturbances in the formation or metabolism of uridine diphosphate glucuronic acid.

roposed Course of Project: We have planned a further study of the properties of UDP-glucose dehydrogenase, especially as to the nature of a recently observed enhancing effect of amino acids on the rate of oxidation. Synthesis of C^{14} labeled active glucuronic acid from C^{14} glycogen (or sucrose) and UTP is now feasible since all the step enzymes can be isolated. We hope to be able to continue our very fruitful collaboration with Dr. Isselbacher on the metabolism of hyaluronic acid and related substances.

Analysis of NIH Program Activities

Budget Data Sheet

IAMD-62115-26
ERIAL NO.

UDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	26,800	2	2	4	2	1½	3½	
FY 1956	29,800	2	3	5	2	3	5	

BUDGET ACTIVITY:

RESEARCH ☒
ADMINISTRATION ☐
REVIEW & APPROVAL ☐
TECHNICAL ASSISTANCE ☐

IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

Dr. Elizabeth Anderson, Postdoctoral Fellow - Am. Cancer Society - Sept. 54-55

Dr. Robert W. Wheat - Postdoctoral Fellow - USPHS - Dec. 54-Nov. 55
Dr. Julius Axelrod, Lab. Chemical Pharmacology, NHI.-73
Dr. M. Pittman, National Microbiological Institute
Dr. W. W. Kielley, National Heart Institute -NIAMD NHI -73
Dr. K. Isselbacher, NIAMD Arthritis and Rheumatism Brance D NIAMD 62131-96
Strominger - Section on Pharm. and Tox. NIAMD-62124-70

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

NIAMD-62115-26
SERIAL NO.

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Metabolism of Uridinediphosphoglucose (UDPGlucose) in Hemophilus Influenza B. Herman M. Kalckar. Acta Chemica Scandinavica 8, 1103 (1954).

The Biological Synthesis and Function of Uridine Polyphosphates. Herman M. Kalckar. Science 119, 479 (1954).

Enzymatic Oxidation of Uridine Diphosphate Glucose to Uridine Diphosphate Glucuronic Acid. J. L. Strominger, H. M. Kalckar, J. Axelrod and E. S. Maxwell. J. Am. Chem. Soc. 76, No. 24 (1954).

LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

C. - 1

Analysis of NIH Program Activities

Project Description Sheet

NIAMD
STITUTE

2. Biochemistry and Nutrition
LABORATORY OR BRANCH

zymes & Cellular Biochemistry
CTION

4. ______________________
LOCATION (IF OTHER THAN BETHESDA

AMD-62115-27
RIAL NO.

Crbohydrate Metabolism in the Spleen and X-Irradiated Mice
OJECT TITLE

Glbert Ashwell
INCIPAL INVESTIGATOR(S)

Jan Hickman
OHER INVESTIGATORS

POJECT DESCRIPTION:

Ojectives: Earlier work has disclosed a marked alteration in the pentose phosphate metabolism of the X-irradiated sucrose spleen. In order to evaluate these observations, a study of the metabolism of ribose phosphate by the normal spleen was undertaken.

Mthods employed: Spleen enzyme preparations are incubated with ribose phosphate and the products isolated by chromatography on ion-exchange resins identified by color reactions and, where possible, by the formation of characteristic derivatives.

Mjor findings: D-xylulose phosphate has been demonstrated as a new intermediate in the metabolism of ribose phosphate. This was the first definitive identification of this ester in plant or animal tissues, although its presence had been presumed in various bacterial systems. Further study of the metabolism of the pentose phosphates has resulted in the tentative identification of a new pentose, erythro-3-ketopentose phosphate, the formation of which is apparently dependent upon the presence of extremely small amounts of copper.

Snificance to Research in Arthritis and Metabolic Diseases: It is expected that knowledge of these pathways will help contribute to an understanding of the pathological effects of X-radiation. These reactions may also be affected in other pathological conditions.

)-62115-27
L NO.

oposed Course of Project: The intermediates described will be isolated in pure form and metabolic pathways of these new compounds studied. The mechanism of the interconversions will be studied with emphasis upon purification of the enzyme systems involved and with attention to the role of metal and other cofactors.

Analysis of NIH Program Activities

Budget Data Sheet

IAMD-62115-27
ERIAL NO.

UDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
Y 1955	15,200	1	1	2	1	1	2	
Y 1956	15,200	1	1	2	1	1	2	

UDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

DENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANI-
ATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER
955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

F THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE
N THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR
UNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

NIAMD-62115-27
SERIAL NO.

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Formation of Xylulose Phosphate from Ribose Phosphate in Spleen Extracts. Gilbert Ashwell and Jean Hickman. J.A.C.S., 76, 5889 (1954).

Spleen ATPase Activity in Irradiated Mice Treated with Spleen Homogenate. W. Smith, W. Anderson, G. Ashwell. Am. J. Physiol., 178, 471 (1954).

LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Analysis of NIH Program Activities

Project Description Sheet

NIAMD
NSTITUTE

2. Laboratory of Biochemistry and Nutrition
LABORATORY OR BRANCH

ractionation and Isolation
ECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NIAMD-62116-28
SERIAL NO.

arge-scale processing of biological material
ROJECT TITLE

. C. Keresztesy
RINCIPAL INVESTIGATOR

THER INVESTIGATOR

ROJECT DESCRIPTION: Large-scale processing of biological material to extract and purify substances of biological importance.

bjectives: Many problems of importance in the biochemistry of disease require the isolation and identification of substances which are present in only trace amounts in the particular biological source. It becomes necessary, in order to obtain sufficient quantities of the desired compound for study, to process large amounts of biological source materials, such as liver, brains, body excretory products, plant materials, etc.

ethods employed: The laboratory is equipped with large-scale apparatus, such as stills, filters, reaction and extraction kettles, etc. In most isolation problems the original small-scale process has to be modified and developed, so that it can be carried out efficiently on the larger scale. This adaptation or process development is an important function of the laboratory. The degree of participation of the laboratory varies according to the needs of the specific problems.

ajor findings: Among the more important operations have been the following: 376 kilos yeastamine and 176 kilos of hog and sheep kidney powder processed for Factor 3 concentrate for Dr. Klaus Schwarz. 990 kilos of rhododendron leaves and 180 kilos of kalmia leaves processed for andromedotoxin for Dr. E. C. Horning (NHI Natural Products Lab.). 240 kilos of bulbs processed for Dr. W. C. Wildman (NHI Natural Products Lab.).

ifnificance to Arthritis and Metabolic Research: Ordinary laboratories lack facilities to effectively carry on studies which require the extraction and processing of large quantities of biological materials. However, with the

equipment and trained personnel of the large-scale laboratory, such investigations as the isolation of Factor 3, can be undertaken and successfully completed.

roposed course of project: Facilities for the safe use of volatile and inflammable solvents are being expanded. When facilities are completed, extraction procedures not possible at present can be carried out. This will increase the number of isolation studies in which the large-scale laboratory can be of help.

Analysis of NIH Program Activities

Budget Data Sheet

NIAMD-62116-28
SERIAL NO.

BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
1955	11,800	1	1	2	2/3	1	1 2/3	
1956	13,100	1	1	2	1	1	2	

BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

DENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANI-
ATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER
955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

Laboratory of Chemistry of Natural Products NHI -113

F THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE
N THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR
UNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

NIAMD-62116-28
SERIAL NO.

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Andromedotoxin. A Potent Hypotensive Agent from Rhododendron Maximum. H. B. Wood, Jr., V. L. Stromberg, J. C. Keresztesy, and E. C. Horning. J.A.C.S. 76, 5689 (1954).

Section on Chemistry of Pyridoxine in Sebrell and Harris's THE VITAMINS Vol. 3, pp. 222-233.

LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

. - 1

Analysis of NIH Program Activities

Project Description Sheet

NIAMD
NSTITUTE

2. Laboratory of Biochemistry and Nutrition
LABORATORY OR BRANCH

ractionation and Isolation
ECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NIAMD-62116-29
SERIAL NO.

icrobiological assays for vitamins and amino acids
ROJECT TITLE

. Silverman
RINCIPAL INVESTIGATOR

. Bakerman, M. Romine and R. Gardiner
THER INVESTIGATORS

ROJECT DESCRIPTION:

jective: The determination of the concentration of various vitamins and amino acids in a variety of materials, such as extracts and concentrates, foodstuffs, body tissues and excretory products, can be carried out by the use of microbiological assays. Under this project samples submitted by investigators on nutritional and allied projects are analyzed for their content of the specific vitamin or amino acid under study.

thods employed: The use of microbiological assays for the determination of folic acid continues to be of major importance in the studies on folic acid.

gnificance to Arthritis and Metabolic Research: These microbiological assay procedures are a very important tool for the measurement of the concentrations of various cell constituents, i. e., amino acids and vitamins.

oposed course of project: With the extension of laboratory findings to clinical investigations, there will be an increasing use of these assays from clinical materials.

C. - 2

Analysis of NIH Program Activities

Budget Data Sheet

NIAMD-62116-29
SERIAL NO.

BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
Y 1955	23,800	2	3	5	1 1/3	3	4 1/3	
Y 1956	26,800	2	4	6	2	3	5	

BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

None

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

NIAMD-62116-29
SERIAL NO.

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

I.C. - 1

Analysis of NIH Program Activities

Project Description Sheet

NIAMD
INSTITUTE

2. Laboratory of Biochemistry and Nutrition
LABORATORY OR BRANCH

Fractionation and Isolation
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA

5. NIAMD-62116-30
SERIAL NO.

Studies on folic acid
PROJECT TITLE

M. Silverman and J. C. Keresztesy
PRINCIPAL INVESTIGATORS

G. J. Koval
OTHER INVESTIGATORS

PROJECT DESCRIPTION:

Studies on folic acid:
(a) Naturally-occurring forms of,
(b) Enzymatic degradation of citrovorum factor,
(c) The urinary compounds associated with folic acid metabolism in the rat.

Objectives: Folic acid, a vitamin of the B complex, has been shown to be needed by most animal species. Its importance and role in the enzyme systems which are related to growth, such as purine synthesis, have become better recognized in the past year. By identifying the natural-occurring forms of folic acid, it will be possible to obtain new anti-folic compounds, other than those used at present to control abnormal growth, specifically leukemia. Similarly, by identifying the products associated with folic acid metabolism in vivo and in vitro, a better understanding of some of the fundamental processes of growth will result.

Methods employed:

(a) The microbiologically-inactive form of folic acid in liver can be converted to the active citrovorum factor form by incubation with liver. The problem is now resolved into preparing suitable extracts of the microbiologically inactive folic acid and fractionating such extracts to obtain the required substance in pure form.

(b) Fractionation of liver extract for the purification of the enzyme which destroys citrovorum factor in the presence of l-glutamic and is being carried out using protein fractionation methods.

Analysis of NIH Program Activities

Budget Data Sheet

NIAMD-62116-30
SERIAL NO.

BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
Y 1955	19,100	2	1	3	2	1	3	
Y 1956	19,100	2	1	3	2	1	3	

BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

None

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

NIAMD-62116-30
SERIAL NO.

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Tables in "Standard Values in Nutrition and Metabolism" 1953 in Handbook of Biological Data, The National Research Council (Tables 138, 139, 147; pages 231, 232, 240). Milton Silverman.

Isolation of N^{10} Formyl Folic Acid. M. Silverman, J. C. Keresztesy, and G. J. Koval. J. Biol. Chem. 211, 53-61 (1954).

Excretion of a Histidine Metabolite by the Rat. M. Silverman, H. A. Bakerman and F. S. Daft. Proc. Soc. Exp. Biol. and Med. 87, 451 (1954).

Isoglutamine and the Growth of Lactobacillus Arabinosus. M. Silverman, M. K. Romine and F. S. Daft. J. Bact. 68, 98-102 (1954).

Synthesis of a Histidine Metabolite. J. E. Seegmiller, M. Silverman, H. Tabor, and A. H. Mehler. J.A.C.S. - December, (1954).

LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Intermediary Metabolism
SECTION

4. Bethesda
LOCATION

5. NIAMD-62117-31
SERIAL NUMBER

6. Study of Gluconic Acid Metabolism
PROJECT TITLE

7. Dr. I. G. Leder
PRINCIPAL INVESTIGATOR

8. None.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objective of this project is to elucidate the mechanism by which gluconic acid is utilized in mammalian tissues.

Methods Employed: The enzyme which catalyzes the initial metabolic step in the utilization of gluconic acid, namely, the reaction gluconic acid   gluconic acid-6-phosphate, is obtained in cell-free extracts and purified. The course of the reaction is followed by oxidizing the product with gluconic acid-6-phosphate dehydrogenase and triphosphopyridine nucleotide, and spectrophotometrically observing the reduction of the latter material.

Major Findings: A reaction between gluconic acid and adenosine triphosphate has been demonstrated in extracts of hog kidney and the corresponding enzyme has been partially purified. The reaction product serves as a substrate for phosphogluconic dehydrogenase; this observation indicates that gluconic acid is phosphorylated in the sixth position by kidney extracts in the presence of adenosine triphosphate.

Significance to NIAMD Research: Although an enzyme which oxidizes glucose to gluconic acid has been isolated from liver, it has been demonstrated that this reaction does not occur to a detectable extent in vivo. However, it has been shown that gluconic acid is metabolized by intact animals. The results of this study will reveal how a non-phosphorylated intermediate is geared to the

9. PROJECT DESCRIPTION - Continued

important phosphorylating pathway of carbohydrate metabolism, and will thus provide further information necessary for an intelligent analysis of derangements in such metabolism.

Proposed Course of Project: The transphosphorylating enzyme obtained from hog kidney will be further purified. After this is accomplished it will be possible to study the reaction stoichiometry, cofactor requirements of the system, and substrate specificity of the enzyme.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD-62117-31
SERIAL NUMBER

1. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	10,600	1	1	2	1	5/6	1 5/6	
FY 1956	12,600	1	1	2	1	1	2	

2. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

3. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

None

4. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

Section on Enzymes and Cellular Biochemistry NIAMD - 62115-23

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD-62117-31
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Intermediary Metabolism
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62117-32
SERIAL NUMBER

6. The Metabolism of Glucuronic Acid
PROJECT TITLE

7. Dr. F. Eisenberg, Jr.; Dr. J.B. Field
PRINCIPAL INVESTIGATORS

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objective of this project is to elucidate the metabolic pathways of formation and utilization of glucuronic acid in animals and men.

Methods Employed: C^{14}-labeled precursors of glucuronic acid are incubated with animal tissue slices in the study of glucuronic acid formation. C^{13}-labeled glucuronic acid and glucuronolactone are administered to patients in the study of glucuronic acid conjugation and incorporation into polysaccharides. In all cases, labeled end products are isolated and the molecular position of isotope determined. From data so obtained, the metabolic pathways traversed by the labeled compounds are deduced.

Major Findings: In the study of glucuronic acid formation it has been found that the immediate precursor of glucuronic acid in the guinea pig is six carbon compound. In the study of glucuronic acid utilization it has been found that glucuronolactone-6-C^{13} administered orally to a human is not incorporated into urinary glucuronide.

Significance to NIAMD: In view of the wide distribution of glucuronic acid in connective tissue, a defect in the metabolism of this compound may in some way be associated with arthritis and other diseases of that tissue. By following its metabolic course with isotopes, some insight should be gained concerning the way in which the normal human handles glucuronic acid. Comparison of results so obtained with those acquired from the study of diseased individuals may provide a clue to the nature of the biochemical lesions involved.

Project Description Sheet Continued

Proposed Course of Project: Recent studies in other laboratories have indicated that glucuronolactone is physiologically different from glucuronate, and that the two molecular species are therefore not easily interconvertiable. The plan for the coming year is to continue the study of labeled glucuronolactone metabolism and to compare it with the fate of labeled glucuronate in normal and diseased states, both with respect to conjugation and incorporation into polysaccharides.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62117-32
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	15,500	1	1½	2½	1	5/6	1 5/6	
FY 1956	16,500	1	1½	2½	1	1½	2½	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO. (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

Section on Enzymes and Metabolism NIAMD 62115-26

R.P.O. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62117-32
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FORM THIS PROJECT DURING CALENDAR YEAR 1954:

"Degradation of Isotopically Labeled Glucose via Periodate Oxidation of Gluconate", by F. Eisenberg, Jr., J. Am. Chem. Soc., 76, 5152 (1954).

"The Formation of Glucose and Glucuronic Acid from Lactate-3-C^{14}", by F. Eisenberg, Jr., J. Biol. Chem., 212, 501 (1954) (in press).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Intermediary Metabolism
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62117-33
SERIAL NUMBER

6. Mechanism of Action of Enzymes. I. The Mechanism of Action of the Phosphohexose Isomerases.
PROJECT TITLE

7. Dr. Yale J. Topper
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objective of this project is to study known enzymes with respect to the detailed chemical mechanism by which they effect transformations of their respective substrates.

Methods Employed: The isomeriaztions effected by the two phosphohexose isomerases are studied in two ways; 1) non-isotopic substrates are exposed to the biological catalysts in the presence of D_2O and the distribution of deuterium in the products is determined; 2) deuterated substrates are isomerized and the redistribution of the isotope is then studied.

Major Findings: In a preliminary study of a phosphohexose isomerase derived from rabbit muscle it has been found that in the conversion of fructose-6-phosphate into glucose-6-phosphate, one atom of carbon-bound deuterium is incorporated into the product when the reaction is carried out in D_2O. This indicates that, just as in the case of the corresponding alkali-catalyzed reaction, the enzymatic interconversion of the two hexoses involves the intermediary formation of an enediol.

Significance to NIAMD: Phosphohexose interconversion os one of the principal steps in carbohydrate metabolism. It is felt that a more detailed understanding of this and other enzymstic reactions will aid in the approach to various metabolic diseases.

Project Description Sheet Continued

Proposed Course of Project: A second phosphohexose isomerase which interconverts fructose-6-phosphate and mannose-6-phosphate has recently been prepared from rabbit muscle by M. Slein. The stereochemical differences in the relationship between the two isomerases and their corresponding substrates will be investigated during the next year.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62117-33
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	13,300	1	1	2	1	5/6	1 5/6	
FY 1956	16,300	1	1	2	1	1	2	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62117-33
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

E.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Intermediary Metabolism
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62117-34
SERIAL NUMBER

6. Humoral Antagonists of Insulin
PROJECT TITLE

7. Dr. J.B. Field; Dr. D. Stetten, Jr.; Technician- Mr. W.J. Smith
PRINCIPAL INVESTIGATORS

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objective of this project is to determine whether the sera of insulin-resistant diabetic patients contain an agent or agents which are responsible for the observed resistance. If so, a purification and characterization of the substance is envisioned.

Methods Employed: The physiological activity of insulin is determined by noting the augmentation of glycogenesis produced in the isolated rat hemi-diaphragm in the presence of the hormone as compared to controls with no added insulin. Using data from such experiments as base-line, the sera obtained from suitable diabetic patients will be assayed for an anti-insulin effect.

Major Findings: The method for assaying insulin activity, using increased deposition of glycogen in rat hemi-diaphragm as a criterion, has been standardized.

Significance to NIAMD: Establishment of the presence of an insulin antagonist in the serum of insulin-resistant diabetics would certainly lead to a deeper understanding of this phenomenon, observed particularly during periods of acidosis and infection.

Proposed Course of Project: The first series of experiments will be concerned with the refinement of the method employed in assaying for insulin activity and in testing for the presence of humoral insulin antagonists. Time will then be devoted to an attempt to fractionate appripriate deabetic sera in order to purify and characterize the agent or agents.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62117-34
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	12,000	1	2/3	1 2/3	5/6	2/3	1½	
FY 1956	16,000	1	1	2	1	1	2	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARRALLES RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERIVCE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

Section on Endocrinolody NIAMD 62114-19

R.P.C. - 3 Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62117-34
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutirtion
LABORATORY

3. Intermediary Metabolism
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62117-35
SERIAL NUMBER

6. Metabolic Disturbances in Creatinuric Diseases
PROJECT TITLE

7. Miss. J.D. Benedict and Dr. D. Stetten, Jr.;
PRINCIPAL INVESTIGATORS

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objectives of this project are: 1) to obtain information on the relationship of vitamin E deficiency in animals to muscular dystrophy; 2) to investigate the creatinuria resulting from thyroxin administration to rabbits; 3) to study several patients exhibiting creatinuria.

Methods Employed: N^{15}-labeled glycine is synthesized and administered orally to patients or to experimental animals. The liver incorporates this substrate into creatine which is then converted to creatinine to a greater or lesser extent, by muscle. Subsequently, these metabolic products are isolated form the urine by means of ion exchange chromatography, and the amounts of isotope they contain are determined and compared.

Major Findings: It has been found that whereas the patient with muscular dystrophy synthesizes creatine at a normal rate, his conversion of this material into creatinine is abnormally low. Thus, the urine of such a patient fed N^{15}-labeled glycine contains creatine having a much higher isotope concentration than the simultaneously excreted creatinine.

Significance to NIAMD:- Creatinuria is one of the prinicpal biochemical manifestations of progressive muscular dystrophy. Thus, a study of the etiology of this lesion in various other physiological states such as vitamin E deficiency and thyrotoxicosis might be expected to aid in the clinical approach to muscular dystrophy.

Project Description Sheet Continued

Proposed Course of Project: 1) Young, vitamin E deficient rabbits will be fed N^{15}-labeled glycine and the isotope concentrations in the simultaneously excreted creatine and creatinine will be compared. 2) The same procedure will be repeated on animals which have been rendered thyrotoxic. 3) Selected patients who exhibit creatinuria will be studied in the same fashion.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62117-35
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	16,800	2	2	4	1 1/3	1 1/6	2½	
FY 1956	22,300	2	2	4	2	2	4	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO. (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLES RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

Section on Endocrinolody NIAMD 62114-16

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62117-35
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

"The Origin of Urinary Creatine in Progressive Muscular Dystrophy", by J.D. Benedict, H.J. Kalinsky, L.A. Scarrone, A.R. Wertheim, and D. Stetten, Jr., J. Clin. Invest. (in press).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

.P.C. - 1
ecember 1954

Analysis of NIH Program Activities

Project Description Sheet

National Institute of Arthritis and Metabolic Diseases
INSTITUTE

Biochemistry and Nutrition
LABORATORY

3. Intermediary Metabolism
SECTION

Bethesda
LOCATION

5. NIAMD-62117-36
SERIAL NUMBER

Metabolism of Glycogen
PROJECT TITLE

Dr. M. R. Stetten; Dr. D. Stetten, Jr.
PRINCIPAL INVESTIGATORS

None
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Objectives: To gain insight into the nature of the normal turnover of the glycogen of liver and muscle.

Methods Employed: Radioactive glucose is administered to animals and subsequently liver and muscle glycogen are isolated. The glycogen obtained is degraded enzymatically by methods designed to split off glucose residues in a systematic fashion and to yield a series of limit dextrins. The fragments are assayed for radioactivity.

Major Findings: Glycogen, although yielding only glucose on total hydrolysis, is metabolically inhomogenous. Glycogen turnover does not consist merely of replacement of preexisting molecules by newly formed molecules. Instead, glucose residues are added to, and removed from, the non-reducing ends at the periphery of the polysaccharide molecule. By a continual process of branching, glucose residues find their way from the peripheral tiers into the more centrally located layers.

Significance to NIAMD Research: Alterations and defects in the way the body metabolizes various carbohydrates have been found to be characteristic of certain nutritional states, drug actions and metabolic diseases such as diabetes and Von Gierke's disease. Any additional knowledge as to how carbohydrates are normally handled may be expected to contribute to a better understanding of the nature of these conditions and diseases.

PROJECT DESCRIPTION - Continued

Proposed Course of Project: Correlation between the size of glycogen molecules and the quantity of glycogen found in liver and muscle after standard periods of fasting and after administration of certain hormones or drugs will be sought. To this end, a method of molecular weight determination involving reaction of carbonyl groups with radioactive cyanide, suggested by Isbell, is being developed. The method may prove useful in the study of other polysaccharides.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

No. NIAMD-62117-36
SERIAL NUMBER

1. BUDGET DATA:

	ESTIMATED ESPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	21,900	1½	1½	3	1 1/3	1 2/3	3	
FY 1956	29,900	2	2	4	2	2	4	

2. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

3. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

None

4. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

5. NIAMD-62117-36
SERIAL NUMBER

6. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

"A Study of the Nature of Glycogen Regeneration in the Intact Animal", by M. R. Stetten, and D. Stetten, Jr., J. Biol. Chem. 207, 331 (1954).

"Glycogen Regeneration in Vivo", by M. R. Stetten and D. Stetten, Jr., J. Biol. Chem., (in press).

7. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Alvarenga Award of Philadelphia College of Physicians - Dr. D. Stetten, Jr.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

National Institute of Arthritis and Metabolic Diseases
INSTITUTE

Biochemistry and Nutrition
LABORATORY

3. Intermediary Metabolism
SECTION

Bethesda
LOCATION

5. NIAMD-62117-37
SERIAL NUMBER

Evaluation of catabolic pathways for glucose in intact cells
PROJECT TITLE

Dr. B. Bloom; Dr. F Eisenberg, Jr.
PRINCIPAL INVESTIGATORS

None
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Objectives: The objectives of this project are: 1) the determination of the extent to which the glycolytic pathway operates in the catabolism of glucose in normal tissue; 2) a comparison of this quantity with the role of the glycolytic pathway in various pathological states.

Methods Employed: The methods employed to date have primarily involved determination of the radiochemical yield of carbon dioxide from various C^{14}-labeled substrates in vitro and in vivo. Also, a simplified technique for the anlysis of C^{14} activities in carbons 1 and 6 of glucose has been developed.

Major Findings: It has been demonstrated that approximately 44% of glucose catabolism in liver slices derived from normal rats proceeds via the glycolytic pathway, and that the remaining 56% of glucose catabolism is consistent with the requirements of the oxidative pathway. It has also been shown that diaphragm sections obtained from normal rats catabolize glucose exclusively through the blycolytic pathway, although this tissue is capable of oxidizing gluconic acid, a product of the oxidative pathway. Furthermore, it has been observed that in liver slices derived from diabetic and fasted rats an increased fraction of glucose is glycolyzed as compared to that catabolized non-glycolytically.

Significance to NIAMD Research: In order to properly evaluate the disturbances in glucose metabolism occurring in thos pathological conditions characterized by abnormal carbohydrate metabolism, it is essential to understand the behavior of glucose in normal cells.

. PROJECT DESCRIPTION - Continued

The program outlined in this report should yield results which will facilitate such understanding.

Proposed Course of Project: To date, work on this project has primarily involved the use of isolated liver and diaphragm. Such studies will be extended to other tissues such as brain, spleen, heart, testes, kidneys, etc. Also certain aspects of this problem will be pursued *in vivo*.

P.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD-62117-37
SERIAL NUMBER

1. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	16,900	1½	1 1/3	2 5/6	1 ½	1 1/3	2 5/6	
FY 1956	20,900	2	1½	3½	2	1½	3½	

2. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

3. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

None

4. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITH NIH)

Section on Enzymes and Cellular Metabolism

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD 62117-37
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

"The Fraction of Glucose Catabolized via the Glycolytic Pathway", by B. Bloom and D. Stetten, Jr., J. Biol. Chem., (in press).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

.P.C. - 1
ecember 1954

Analysis of NIH Program Acticities

Project Description Sheet

National Institute of Arthritis and Metabolic Diseases

Chemistry
LABORATORY

3. Carbohydrates
SECTION

Bethesda
LOCATION

5. NIAMD- 62118-38
SERIAL NUMBER

New Analgesic Agents Derived from Thebaine
PROJECT TITLE

Lyndon F. Small
PRINCIPAL INVESTIGATORS

None
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Continuation of studies on new narcotics derived from action of methyl and ethyl hypobromite on thebaine. Extended to analogous reactions of dihydrothebaine and dihydrocodeinone enol acetate, which would not be expected to react but nevertheless do so.

By invitation of the Secretary General of United Nations served on Committee of three international experts on origin of opium, United Nations, N. Y.

Completed remaining portion of antimalarial research and published results.

.P.C. - 2
ecember 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAID- 62118-38
SERIAL NUMBER

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	15,700	1	1	2	1	1	2	
FY 1956	15,700	1	1	2	1	1	2	

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12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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3. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

None

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4. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD- 62118-38
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Lewis J. Sargent and Lyndon F. Small. Carbinolamines derived from 7- and 8-Acetyl-1,2,3,4-tetrahydroacridines as Plasmodicides. J. Org. Chem., 19, 1400 (1954).

7. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Laboratory of Physical Biology
LABORATORY OR BRANCH

3. Physiology
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NIAMD- 62129-39
SERIAL NO.

6. The effect of roentgen radiation on tissue growth and differentiation
PROJECT TITLE

7. Helen D. Park
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To study patterns of growth and differentiation in simple tissues after various doses of roentgen radiation.

Methods Employed: Hydra, a fresh water coelenterate, has been used in these studies because of its ability to regenerate (differentiate) lost parts and because during asexual reproduction growth phases can be relatively easily separated from differentiative phases of development.

Major Findings: Three major findings of the past year have been (1) that $MgSO_4$ and glutathione together when added to an inorganic medium protect hydras against the reproduction-inhibiting effects of roentgen radiation. The protective effect is potentiative and not additive. It seems particularly significant that protection results when the two agents are given after irradiation. (2) That a dose of roentgen rays which is lethal to 72% of adult animals in 24 hours kills only 19% of their newly developed offspring. This difference in sensitivity apparently does not exist at sub-lethal doses when reproduction is used as a criterion. (3) That roentgen radiation is more effective in preventing the initiation of development than in interference with morphogenesis once development has started.

9. PROJECT DESCRIPTION - CONTINUED

Significance to NIAID Research: These studies show that it is possible to separate radiation effects on growth and morphogenesis and partly, at least, to counteract radiation effects by chemical means. They also illustrate the use of a relatively simple, asexually reproducing animal to obtain information about factors that affect tissue growth in general.

Proposed course of project: (1) To study the time sequence in which Mg^{++} and GSH exert their effects. (2) To study the effect of single and repeated low doses of ionizing radiations on the course of tissue growth and differentiation. The direction of this project will be shifted gradually to problems of metabolism and growth.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD- 62129-89
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	6,100	1		1	1		1	
FY 1956	6,100	1		1	1		1	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 10)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL No.(S) IF WITHIN NIH)

None

R.P.C. - S
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD- 62129-39
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Daniel, G. E. and H. D. Park. A protective effect of inorganic magnesium against X-ray damage to hydra. Am. J. Roentg., Radium Therapy & Nuclear Med., 72: (5) 857-866, Nov., 1954.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

.P.C. - 1
ecember 1954

Analysis of NIH Program Activities

Project Description Sheet

. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

. Chemistry
LABORATORY

3. Carbohydrates
SECTION

. Bethesda
LOCATION

5. NIAMD- 62118-39
SERIAL NUMBER

. Higher-carbon sugars, anhydro sugars, sugar alcohols and their derivatives
PROJECT TITLE

. N. K. Richtmyer
PRINCIPAL INVESTIGATORS

. J. W. Pratt, L. C. Stewart, E. Zissis
OTHER INVESTIGATORS

. PROJECT DESCRIPTION

Objectives: To evolve generalizations relating the physical properties of the groups of substances named in the project title to their configurations and conformations.

Recent Progress: The synthesis from D-allose, by a combination of chemical and biochemical methods, of six new crystalline heptoses, heptuloses, and heptitols; evidence that not only sugars with the *altro*-, *gluco*-, *ido*-, and *gulo*-configurations but also those with the *allo*-, *manno*-, *talo*-, and probably the *gala*-configurations form monomeric nonreducing anhydrides in acid solution; isolation of anhydrides thus formed from D-allose, L-*allo*-heptulose, 3-deoxy-D-*arabino*-hexose, D-*gluco*-heptulose, D-*manno*-heptulose, D-*talo*-heptulose, and a second anhydride from D-*altro*-heptulose; two syntheses of 1,5-anhydro-D-altritol; and proof of structure of the methyleneation products of D-arabitol.

Current and Projected Investigations: Proof of structure of the new anhydro sugars and extension of the reaction to additional sugars; also extension of the studies on sugar alcohols and their anhydrides and acetals.

P.C. - 2
cember 1954

Analysis of NIH Program Activities

Budget Data Sheet

. NIAMD- 62118-39
SERIAL NUMBER

. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	38,600	4	2	6	4	2	6	
FY 1956	38,600	4	2	6	4	2	6	

. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

None

. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

None

.P.C. - 3
ecember 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

5. NIAMD- 62113-39
SERIAL NUMBER

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5. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Emmanuel Zissis and Nelson K. Richtmyer. O-Methylene and Other Derivatives of D-Arabitol (Synonym, D-Lyxitol), 1-Deoxy-D-arabitol and 1-Deoxy-D-lyxitol. J. Am. Chem. Soc., 76, 5515-5522 (1954).

Laura C. Stewart and Nelson K. Richtmyer. The Formation of 1,6- and 1,7-Anhydro-D-glycero-β-D-gulo-heptopyranoses from D-glycero-D-gulo-Heptose in Acid Solution. J. Am. Chem. Soc. (in press).

Laura C. Stewart and Nelson K. Richtmyer. Transformation of D-Gulose to 1,6-Anhydro-β-D-gulopyranose in Acid Solution. J. Am. Chem. Soc. (in press).

James W. Pratt and Nelson K. Richtmyer. Transformation of D-Allose to 1,6-Anhydro-β-D-allopyranose in Acid Solution. J. Am. Chem. Soc. (in press).

. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Nelson K. Richtmyer elected Chairman of the Division of Carbohydrate Chemistry of the American Chemical Society, 1954.

Analysis of NIH Program Activities

Project Description Sheet

National Institute of Arthritis and Metabolic Diseases
INSTITUTE

Chemistry
LABORATORY

3. Carbohydrates
SECTION

Bethesda
LOCATION

5. NIAMD- 62118-40
SERIAL NUMBER

Microanalytical Laboratory
PROJECT TITLE

W. C. Alford
PRINCIPAL INVESTIGATORS

Mary Jean Barnett, guest, Paula M. Parisius, Evelyn G. Peake, Byron Baer, C. G. Remsburg, and W. M. Jones
OTHER INVESTIGATORS

PROJECT DESCRIPTION

The microanalytical laboratory is a service organization which provides many necessary analytical services for research personnel of the National Institutes of Health. The scope of this work is summarized as follows:

1. From 8,000 to 10,000 elemental or functional group determinations are made annually. These include carbon, hydrogen, nitrogen, sulfur, chlorine, bromine, iodine, phosphorus, metals and various functional groups such as acetyl, active hydrogen, methoxyl, carboxyl, etc. Service of this type is routinely provided for approximately 100 research workers of the NIH staff. In addition, analyses are performed for governmental agencies outside the NIH, insofar as they can be handled without jeopardizing the progress of NIH research. For example, during the past year several hundred analyses have been done for personnel of the Naval Medical Research Institute, Bethesda, Md., The Tuberculosis Research Laboratory, USPHS, New York, and the National Bureau of Standards. Other agencies which have at various times received needed services include: The Naval Research Laboratory, Anacostia, Chemical Warfare at Camp Dietrich, Md., Food and Drug Administration, Washington, D. C., and the Maryland State Health Department.

2. A laboratory operated by Mr. Jones provides infrared spectra for the Carbohydrates Section of the Laboratory of Chemistry. This laboratory was established late in 1954 and is providing, at present, about 70 infrared spectra per month. This number will undoubtedly be increased as conditions become stabilized.

3. The services of Mr. Remsburg are available for various micro and macro analyses. For example, during the past year he has made over 2,000 determinations of lactic acid and phosphorus for Dr. Du Buy of NMI.

4. Consulting service is available to persons having special analytical problems which the laboratory is not equipped to handle. For example, technicians have been instructed in techniques and assisted in setting up apparatus for doing large numbers of micro Kjeldahl nitrogen analyses.

Significance to NIAMD and NIH: The work done by the microanalytical laboratory is of vital importance to many research scientists. The analyses aid in identifying unknown synthetic or natural products; provide proof of purity and identity of synthetic materials; and provide information needed to follow the progress of various research programs. Satisfactory elemental analyses are required for publications describing the synthesis of new compounds.

Proposed Course of Project: It is contemplated that this service will be continued and expanded in every way possible.

P.C. - 2
cember 1954

Analysis of NIH Program Activities

Budget Data Sheet

0. NIAMD-62118-40
SERIAL NUMBER

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1. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	33,300	2	4	6	2	4	6	
FY 1956	33,300	2	4	6	2	4	6	

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1. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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1. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

The National Heart Institute has provided the salary of Mrs. Mary Jean Barnett (GS-9) during the past year.

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1. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

None

P.C. - 3
cember 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

. NIAMD-62118-40
SERIAL NUMBER

. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Carbohydrates
SECTION

4. Bethesda
LOCATION

5. NIAMD- 62118-41
SERIAL NUMBER

6. Ribose Derivatives
PROJECT TITLE

H. G. Fletcher, Jr.
PRINCIPAL INVESTIGATORS

R. K. Ness
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Objectives: To elucidate the chemistry of the sugar ribose with the object of developing methods for the synthesis of biologically important ribosides.

Methods Employed: Guided by the theory of the interactions of atomic groups within molecules, a large variety of chemical methods have been used.

Major Findings: Methods developed earlier in this project for the synthesis of ribopyranosides and ribofuranosides from ribose itself have, in our hands, led also to ribose orthoester derivatives of unique structure. Because of the vital part played by ribose and its derivatives in living organisms it seemed wise to expand our knowledge of ribose through investigation of these orthoesters. 1,2(1-benzyloxybenzylidene)-α-D-ribopyranose has been synthesized in crystalline form and shown to decompose spontaneously into a substance which was proven to be 1,2,4-orthobenzoyl-α-D-ribopyranose.

Significance to NIAMD Research: Understanding of the chemistry of ribose has been increased.

Proposed Course of Project: The behavior of orthoacid derivatives of ribofuranose will be studied further and the information thus gained applied in an investigation of the synthesis of a moiety of the DPN molecule, the so-called "nicotinamide riboside."

I.P.C. - 2
ecember 1954

Analysis of NIH Program Activities

Budget Data Sheet

0. NIAMD- 62118-41
SERIAL NUMBER

1. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	21,800	1½	2	3½	1½	2	3½	
FY 1956	21,800	1½	2	3½	1½	2	3½	

2. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

3. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

None

4. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

.P.C. - 3
ecember 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

.5. NIAMD- 62118-41
SERIAL NUMBER

6. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Ribose Research

Hewitt G. Fletcher, Jr., and Robert K. Ness. Preparation and Properties of 2,3,4-Tri-*O*-benzoyl-β-D-ribose. J. Am. Chem. Soc., 76, 760 (1954).

Robert K. Ness, Harry W. Diehl and Hewitt G. Fletcher, Jr. New Benzoyl Derivatives of D-Ribofuranose and *aldehydo*-D-Ribose. The Preparation of Crystalline 2,3,5-Tri-*O*-benzoyl-β-D-ribose from D-Ribose. J. Am. Chem. Soc., 76, 763 (1954).

Robert K. Ness and Hewitt G. Fletcher, Jr. Preparation and Properties of 3,5-Di-*O*-benzoyl-1,2-*O*-(1-hydroxybenzylidene)-α-D-ribose, an Orthobenzoic Acid Derivative of D-Ribofuranose. J. Am. Chem. Soc., 76, 1663 (1954).

Byproducts

R. Allerton and Hewitt G. Fletcher, Jr. The Acetolysis of Some Carbohydrate Benzyl Ethers. J. Am. Chem. Soc., 76, 1757 (1954).

Hewitt G. Fletcher, Jr., Harry W. Diehl and Robert K. Ness. Methyl β-D-Gulofuranoside and Certain Other Derivatives of D-Gulose. J. Am. Chem. Soc., 76, 3029 (1954).

1. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

National Institute of Arthritis and Metabolic Diseases
INSTITUTE

Chemistry LABORATORY	3. Carbohydrates SECTION
Bethesda LOCATION	5. NIAMD- 62118-42 SERIAL NUMBER

Structure of the Carbohydrate Moieties in Stevioside
PROJECT TITLE

H. G. Fletcher, Jr.
PRINCIPAL INVESTIGATORS

H. B. Wood, Jr. (Fellow)
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Objectives: The objective of this project is to elucidate the structure of the carbohydrate moieties in stevioside, the sweet, non-toxic principle of the Paraguayan plant Stevia Rebaudiana.

Methods Employed: A variety of chemical degradative methods are employed — oxidation with glycol-cleaving agents, methylation, hydrolysis, etc.

Major Findings: Two of the glucose residues in stevioside are joined together by a C_1-C_2 linkage and thence to an alcoholic oxygen of the aglucon. The remaining glucose unit is attached at C_1 to a sterically hindered carboxyl of the aglucon. On treatment with alkali the latter group is cleaved to give levoglucosan and steviolbioside. Thus stevioside is a wholly new type of alkali labile glycoside.

Significance to NIAMD Research: Basic information regarding the structure of the sweetest naturally occurring substance has been gained.

Proposed Course of Project: The synthesis of glucose derivatives esterified at C_1 by sterically hindered acids (i.e. models of stevioside) is being studied by way of confirming our theory regarding the behavior of stevioside with alkali. This work will be completed within the coming year.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD- 62118-42
SERIAL NUMBER

1. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	9,100	½	1	1½	½	1	1½	
FY 1956	9,100	½	1	1½	½	1	1½	

2. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

3. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

None

. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD-62118-42
SERIAL NUMBER

.6. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

H. B. Wood, Jr., R. Allerton, H. W. Diehl and H. G. Fletcher, Jr. Stevioside: The Structure of the Glucose Moieties.

H. B. Wood, Jr. and H. G. Fletcher, Jr. The Anomeric 2,3,4,6-Tetra-O-acetyl-1-(2,4,6-trimethylbenzoyl)-D-glucopyranoses and Their Behavior with Alkali.

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1. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.F.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Carbohydrates
SECTION

4. Bethesda
LOCATION

5. NIAMD- 62118-43
SERIAL NUMBER

6. Labile Metabolites of Amino Acids
PROJECT TITLE

7. B. Witkop
PRINCIPAL INVESTIGATORS

8. L. Cohen
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Project: Development of synthetic and analytical procedures to prove the presence of novel intermediates in the catabolism of amino acids which are too labile to be detected by customary routine methods.

Objectives: To show that a detailed knowledge of the oxidation mechanisms of heterocyclic, aromatic and aliphatic model compounds makes possible the synthesis of missing or novel intermediates in the breakdown of physiologically important factors such as amino acids, purines, vitamins etc. The availability of such intermediates obtained by synthesis makes it possible for the biochemist to gain new insight into metabolic processes.

Methods Employed: New routes are being developed for the synthesis of compounds which so far have not been synthesized because the difficulties encountered have been too great or because the knowledge for the postulation of such compounds has been lacking. Special new techniques are employed in an attempt to simulate in vitro normal and abnormal oxidation processes occurring in vivo. Physico-chemical methods are being used and adapted to the study of the more subtle aspects of reactions and interactions of functional groups in model compounds as well as in higher molecular complexes.

Major Findings: In collaboration with Dr. A. Ek, Bowling Green State University, and Dr. S. Udenfriend (NHI), new labile metabolites derived from tryptophan and bearing oxygen functions in positions 5 and 7 have been prepared and correlated with regard to their actual and potential significance in various biological systems. 5- And 7-hydroxytryptophan, -tryptamine and -(hetero)auxin have been prepared in good yield. The availability of these synthetic substances made possible various biochemical tests and the identification of some of the compounds with new metabolites of tryptophan. In collaboration with Dr. Beiler,

Stetson University, the fundamental mechanism of non-enzymatic transamination has been studied in several ways. The findings have been published in a first programatic paper.

Infrared spectrophotometric methods have been developed for the diagnosis of (labile) heterocyclic and open compounds.

The conversion of histidine (with Dr. Beiler) to (allo)hydroxyproline via the new (allo)-hydroxyornithines has furnished valuable information on stereochemical interrelations and the mechanism of cyclization of open (hydroxy)amino acids into new and known cyclic amino acids.

The transannular interaction of a peptide group has been demonstrated in a model compound for the first time in collaboration with Dr. L. Cohen.

New analytical procedures for the detection of unusual amino acids in microgram quantities have been developed in collaboration with Dr. K. Piez, NIDR.

Significance to Metabolic Diseases Research: Very recent biochemical and clinical investigations have led to surprising findings concerning the etiology of certain long-known diseases. Hereditary, nutritional or environmental factors produce deviations from standard metabolic patterns of amino acid degradation. In particular the following diseases have been associated with new or known amino acid metabolites: schizophrenia and other mental disorders, diabetes, and phenylpyruvic oligophrenia.

Further correlations between amino acid metabolites and certain dysfunctions are not as clear-cut, but certain mental disorders seem to respond to large doses of glutamic acid or glutamine, possibly also to formimidoglutaric acid (from histidine), certain hemophilic cases lack serotonin in the blood platelets, disorders in collagen metabolism may point to abnormal oxidation products of (hydroxy)-proline. In view of all these observations there is a definite necessity for the synthesis of the various missing labile amino acid metabolites whose existence or importance can no longer be doubted. A later expansion of this program may have to deal with raising this type of research to the level of peptides and proteins.

Significance to Arthritis: The new analytical procedures for the detection of unusual amino acids when applied to samples of connective tissue of normal and pathological origin will answer a problem of long standing, i.e., are pathological changes in connective tissue accompanied by chemical changes?

Proposed Course of Project: Further effective research following these lines will be attempted on a scale commensurate with the present facilities.

.P.C. - 2
ecember 1954

Analysis of NIH Program Activities

Budget Data Sheet

NIAMD- 62113-43
SERIAL NUMBER

BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	14,200	2		2	2		2	
FY 1956	20,200	3	2	5	3	1	4	

BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

Dr. S. Udenfriend (NHI)
Dr. K. Piez (NIDR)
Dr. A. Ek, Bowling Green State University
Dr. T. Beiler, Stetson University

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

None

.P.C. - 3
ecember 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

5. NIAMD- 62118-43
SERIAL NUMBER

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6. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

B. Witkop. Rearrangements de Cetones, Alcamines, Peroxydes, Ozonides et Alcaloides dans la Serie de L'Indole. Bull. Soc. Chim., 423 (1954).

B. Witkop. Infrared Diagnosis of the Hydrochlorides of Organic Bases. I. Spectrophotometric Differences between Aminoheterocyclic Bases and their Salts. Experientia, 10, 420 (1954).

B. Witkop. Oxidation Mechanisms. XIV. The Reaction of trans-Decahydroquinoline with Molecular Oxygen. Experientia, 10, 419 (1954).

A. Ek and B. Witkop. The Synthesis of Labile Hydroxytryptophan Metabolites. J. Am. Chem. Soc., 76, 5579 (1954).

B. Witkop and T. W. Beiler. Studies on Schiff Bases in Connection with the Mechanism of Transamination. J. Am. Chem. Soc., 76, 5589 (1954).

B. Witkop. Infrared Diagnosis of the Hydrochlorides of Organic Bases. II. The Structure of Myosmine. J. Am. Chem. Soc., 76, 5597 (1954).

S. Goodwin and B. Witkop. Chemistry of Dihydroxyfumaric Acid. J. Am. Chem. Soc., 76, 5599 (1954).

B. Witkop and J. Patrick. Aspidospermine. II. J. Am. Chem. Soc., 76, 5603 (1954).

B. Witkop, S. Goodwin and T. W. Beiler. 5-Hydroxy-5-hydroperoxybarbituric Acid (Alloxan Hydroperoxide) and Other Alloxan Adducts. J. Am. Chem. Soc., 76, 5813 (1954).

J. B. Patrick and B. Witkop. Oxidation Mechanisms. XV. The Conversion of Benzoxazine Hydroperoxides into the Parent Benzoxazines. J. Org. Chem., 19, 1824-1829 (1954).

B. Witkop. Some Novel Aspects of the Chemistry of Enediols. Angew. Chemie, 66, No. 23, December 1954.

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1. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Analgesics
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62119-44
SERIAL NUMBER

The Syntheses of Compounds Related structurally to Morphine
PROJECT TITLE

E.L. May and James G. Murphy
PRINCIPAL INVESTIGATORS

None
OTHER INVESTIGATORS

PROJECT DESCRIPTION:

Objective: To synthesize pain-relieving and/or sedative drugs which lack or exhibit minimal deleterious side-effects, particularly addiction potential, respiratory depression and nausea.

Methods Employed: Principally, two lines were followed in carrying out this project. In the first a simple desoxy analog (I) (1,5-Dimethyl-6:7-benxmorphan) of the potent analgesic dromoran (II) Dromoroan 3-Hydroxy-N-methylmorphinan) was synthesized in an 11-step process starting from phenylacetonitrile or by a 6-step sequence from B-tetralone. This project, started in 1954, was completed in the early part of 1954.

In the second, a phenolic hydroxyl group was introduced into the benzene portion of (III)(2-Methyl-5-phenylmorphan, a compound previously synthesized by us and found to have fair analgesic activity) to give the substance (IV) (m-Acetoxy, hydroxy, or methoxy 2-methyl morphan). This synthesis was accomplished in an 11-step scheme starting from m-hydroxybenzaldehyde. The known procedure for preparing 2-m-methoxyphenylcyclohexanone, and intermediate, had to be modified for adaptation to large-scale runs inasmuch as large amounts of IV were needed for studies in the monkey. Compounds III and IV might be looked upon as bicyclic meperidine types.

Major Findings: Screening of the substances mentioned above as well as some derivatives and intermediates (Nathan B. Eddy and staff) showed that Compound I and three related substances were one-half to one-third as effective as meperidine in producing analgesia in mice but less toxicbby subcutaneous route of administration. Orally, I was twice as effective as meperidine. Compound IV and its)-acetyl derivative were not only ten times as active as III but much less toxic: they are as potent as morphine (in mice). Further-

Project Description Sheet Continued

more, IV did not exhibit the Straub reaction in mice until ten times the analgesic dose was reached, whereas morphine produces this effect well below the effective dose. Dr. Eddy has judged this compound to be worthy of further (addiction) studies in monkeys.

Course of Projects: Durning the calendar year 1955, it is planned to modify the structure of the highly active compound IV in such a was as to have a 7-membered N-containing ring in place of the 6-membered or piperidine ring. This seems warranted because in the less-active meperidine series, such a modification by other investigators, produced analgesics that appear to have no addiction potential. In addition, the resolution of IV into its opitcal antipodes is projected; it is anticipated that the levoisomer is responsible for most or probably all of the activity of IV. Finally, structural alterations of I and derivatives (which have a more favorable therapeutic ratio than III) such as the introduction of a m-phenolic group, and/or a 10-methyl substituent, and the increase of the N-containing ring size are now in progress.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62119-44
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	10,500	1 1/6		1 1/6	1 1/6		1 1/6	
FY 1956	10,500	1 1/6		1 1/6	1 1/6		1 1/6	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

3. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO. (S)

None

4. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62119-44
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Structures Related to Morphine. I. 2-(2-Dimethylaminoethyl)-2-Phenylcyclohexanone and Derivatives. J.G. Murphy and E.L. May, J. Org. Chem., 19, 615 (1954).

Structures Related to Morphine. II. An Isomer of N-Methylomorphinan. E.L. May and J.G. Murphy, J. Org. Chem., 19, 618 (1954).

Synthesis of 6-Dimethylamino-4,4-Diphenylheptane and other Compounds Related to Methadone. T.D. Perrine and E.L. May, J. Org. Chem., 19, 773 (1954).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Participated in a panel symposium on "Hypontics and Sedatives" at the 8th Post Graduate Assembly of the New York State Society of Anesthesiologists in December. The subject of my talk was "Recent Developments in the Field of Analgesia".

.P.C. - 1
ecember 1954

Analysis of NIH Program Activities

Project Description Sheet

National Institute of Arthritis and Metabolic Diseases
INSTITUTE

Chemistry
LABORATORY

3. Analgesics
SECTION

Bethesda
LOCATION

5. NIAMD- 62119-45
SERIAL NUMBER

The synthesis of the isomeric dihydrothebaine degradation products: 3,4,4-triethyl-5, 6-dimethoxytetrahydronaphthalene and 3-propyl-4-ethyl-4-methyl-5, 6-dimethoxytetrahydronaphthalene.
PROJECT TITLE

Dr. Lewis J. Sargent
PRINCIPAL INVESTIGATOR

None
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Objectives: The preparation of the above-named compounds would complete the second half of a model experiment designed to elucidate the chemical structure of the important morphine derivative - metopon.

Methods Employed: Starting with the newly synthesized key compound -ethyl- (2-chloro-4,5-dimethoxyphenyl)-butyric acid, 3,4-diethyl-6-(2-chloro-4,5-dimethoxyphenyl)-3-hexanol was prepared. Numerous attempts to cyclize the latter to the desired naphthalene derivative failed and led, instead, to the corresponding unsaturated hexene derivative. Despite the use of rather rigorous conditions, the latter substance also resisted cyclization (for steric reasons?) and was recovered largely unaltered.

In another approach, the above key butyric acid was cyclized to the expected tetrahydronaphthalenone which, after treatment with ethyl magnesium bromide and catalytic dehalogenation afforded 3-ethyl-4-ethyl-4-hydroxy-5,6-dimethoxy tetrahydronaphthalene. This substance differs from one of the desired degradation products only in having a hydroxyl in place of an alkyl group on the geminal carbon-4. The replacement of the hydroxyl by ethyl will be studied.

A third, and what appears to be the most promising, approach originated with 7,8-dimethoxytetralone-2. It has been possible, by utilizing a two step process, to dialkylate carbon-1 to yield

PROJECT DESCRIPTION - Continued

1-ethyl-1-methyl-7,8-dimethoxytetralone-2. Apart from steric difficulties, the latter should be convertible to the corresponding tertiary carbinol (via propyl magnesium bromide or propyl lithium) which upon dehydration and hydrogenation of the resulting olefin should lead to one of the two isomeric degradation products.

A fourth pathway utilizing the free-radical induced addition of maleic anhydride to 3-(2,3-dimethoxyphenyl) pentane has been examined cursorily. Results thus far indicate that upon working out proper reaction conditions, this method may prove to be of value too.

Significance to Analgesic Research: Clinical studies have demonstrated that metopon may be a more powerful analgesic than morphine with less addiction liability. Since one of the most important goals of analgesic research is complete divorce of the physical dependence liability from analgesic potency, exact knowledge regarding the structure of metopon may serve to suggest other avenues of research insofar as (a) modifying the morphine molecule or (b) synthesizing related substances are concerned.

Proposed Course of Project: The four approaches outlined above will be thoroughly investigated and, should the need arise, other methods will be devised and studied.

Completed remaining portion of antimalarial research and published results.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD- 62115-45
SERIAL NUMBER

11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	10,100	1		1	1		1	
FY 1956	10,100	1		1	1		1	

12. BUDGET ACTIVITY:

RESEARCH ☒
REVIEW & APPROVAL ☐
ADMINISTRATION ☐
TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

None.

.P.C. -3
ecember 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

5. NIAMD- 62119-45
SERIAL NUMBER

6. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Sargent, Lewis J. The Synthesis of 1-Ethyl-, 2-Ethyl-, 3-Ethyl- and 4-Ethylacridine. J. Org. Chem., 19, 599 (1954)

Sargent, Lewis J., and Small, Lyndon F. Carbinolamines Derived from 7- and 8-Acetyl-1,2,3,4-tetrahydroacridines as Plasmodicides. J. Org. Chem., 19, 1400 (1954)

7. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None.

.P.C. - 1
ecember 1954

Analysis of NIH Program Activities

Project Description Sheet

. National Institute of Arthritis & Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Analgesics
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62119-46
SERIAL NUMBER

6. The Synthesis of 6-Amino-4,4-Diphenyl-3-Heptanone, the Primary Amine Corresponding to Methadone
PROJECT TITLE

7. E.L. May
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objective: To synthesize the title compound above for metabolic studies designed to shed light on tolerance, physical dependence, etc., of narcotics.

Methods: Although several approaches for synthesizing this new compound have been tried, none has yet proved successful. The major obstacle appears to be the great facility with which necessary intermediates cyclize to pyrrolidine derivatives. A new sequence of reactions is now being investigated which involves protection of sensitive centers in the intermediate molecules. For example, the ethylene ketal (I) 1,1-Diphenyl-2-butanone ethylene ketal, is being prepared as an intermediate. This work will continue.

.P.C. - 2
ecember 1954

Analysis of NIH Program Activities

Budget Data Sheet

0. NIAMD - 62119-46
SERIAL NUMBER

1. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	2,600	1/3		1/3	1/3		1/3	
FY 1956	2,600	1/3		1/3	1/3		1/3	

2. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

3. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

None

4. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

5. NIAMD - 62119-46
SERIAL NUMBER

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6. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

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7. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

.P.C. - 1
ecember 1954

Analysis of NIH Program Activities

Project Description Sheet

. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

. Chemistry
LABORATORY

3. Analgesics
SECTION

. Bethesda
LOCATION

5. NIAMD - 62119-47
SERIAL NUMBER

. Chemical Structure and Analgesic Action
PROJECT TITLE

. Nathan B. Eddy
PRINCIPAL INVESTIGATOR

. None
OTHER INVESTIGATORS

. PROJECT DESCRIPTION:

Objectives: To ascertain chemical structure essential for analgesic action, and as far as possible, differentiate them from the chemical features related to toxic effects and addiction liability of the same compounds. This is a part of the over-all attempt to obtain better pain relief with less accompanying toxic reactions and addiction liability.

Methods Employed: By the hot plate method elaborated in this laboratory, compounds of many chemical types and within groups essentially related one to another, are assessed for analgesic action. As a corollary of the investigation, toxicity of active compounds is determined. We are also attempting to ascertain the underlying reasons for peculiar and striking differences in effectiveness of similar compounds when given orally or subcutaneously. The compounds evaluated are from many sources. For sources of materials studied, see item 13. This is, of cours, a continuing project which has been going on for years and only tentative conclusions can be drawn at any particular time. These are currently being assembled as a collaborative endeavor (see item 17.) But a most important development in the investigation of compounds made by our own chemist is the demonstration in a member of the group of analgesic action equivalent to that of morphine. This group of compounds may in a sense be considered as intermediary in the synthesis of morphine. Hence, this finding becomes most important to the over-all objective. Additional quantities of the compound are being propared for addiction liability studies.

.P.C. - 2
ecember 1954

Analysis of NIH Program Activities

Budget Data Sheet

O. NIAMD - 62119-47
SERIAL NUMBER

1. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	27,900	1 1/6	3	4 1/6	1 1/6	3	4 1/6	
FY 1956	27,900	1 1/6	3	4 1/6	1 1/6	3	4 1/6	

2. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

3. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO. (S)

None

4. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARRALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) WITHIN NIH)

None

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December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62119-47
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Leimbach, Dorothy and Eddy, Nathan B.

Synthetic analgesics III. Methadols, isomethadols and thier acyl derivatives.

J. Pharmacol. & Exper. Therap., 110: 135-147, 1954

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Temporary Consultant to the World Health Organization to prepare report referred to in collaboration with a representative from the Narcotic Division of the United Nations.

Chairmanship of panel discussion, Postgraduate Assembly of the New York State Society of Anesthesiologists, Hoetl New Yorker, N.Y., December 11, 1954. (Due to illness, Dr. Charles G. Zubrod substituted as chairman for Dr. Eddy.)

[illegible]
December 1954

Analysis of NIH Program Activities

Program Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Analgesics
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62119-48
SERIAL NUMBER

6. Study of Analgesic Action in Humans with Patholigical Pain
PROJECT TITLE

Nathan B. Eddy
PRINCIPAL INVESTIGATOR

Joseph Cochin
OTHER INVESTIGATOR

PROJECT DESCRIPTION:

Objectives: a) To determine efficacy of new agents and their relative freedom from undesirable side effects in patients with various types of pain, as a part of the over-all effort to improve drug relief of pain.

b) All effective analgesics for severe pain at present are addicting agents. Evidence is available that it may be possible to retain analgesic effectiveness and hold in abeyance tolerance and addiction liability by the simultaneous use of so-called antagonists. We propose to test the practicability and efficacy of such a procedure. It would be of material advantage to the over-all effort of better drug relief of pain.

Methods Employed: By the use of the double-blind technique, randomized administration of a standard analgesic, a placebo, and the new potentially valuable analgesic agent, drugs will be administered to patients with persistent pain in a series of five as coded samples, where the pain is persistent enough to permit the administration of two such series of five. Only one dose of the coded material is given per day, sandwiched between routine drug administration for pain relief. All observations of severity of pain and degree of pain relief and incidence of undsirable side effects will be made by an impartial observer.

For determination of the effect of antagonists on tolerance and dependence development, again using as far as possible, the double-blind technique, paired patients without previous material narcotic experience, but with persistent pain, will be given either a standard analgesic alone, or the same analgesic at the same dose, simultaneously with a selected amount of antagonist. There will be periodic determination of the degree of tolerance and dependence present in each of the patients. Terminal cancer patients specially admitted for this purpose will be the most suitable clinical material.

[illegible]
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62119-48
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	15,300	1 1/3	½	1 5/6	1 1/3	½	1 5/6	
FY 1956	15,300	1 1/3	½	1 5/6	1 1/3	½	1 5/6	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62119-48
SERIAL NUMBER

6. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

7. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

National Institute of Arthritis and Metabolic Diseases
INSTITUTE

Chemistry
LABORATORY

3. Analgesics
SECTION

Bethesda
LOCATION

5. NIAMD- 62119-49
SERIAL NUMBER

The study of the three-dimensional aspect of certain tropane alkaloids
PROJECT TITLE

Stephen P. Findlay
PRINCIPAL INVESTIGATOR

None
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Objectives: The preparation of appropriate derivatives of medically useful plant alkaloids, the search for better methods of synthesizing important plant alkaloids, the isolation of plant alkaloids not yet investigated and the conduct of such other investigations as promise results of particular significance to fundamental or to applied chemistry.

The object immediately in view is the preparation and differentiation of the two unknown stereoisomers of the narcotic, cocaine.

Methods Employed: The methods employed in the investigations of the past year were those typical of research in organic chemistry.

Major Findings: The major finding of this project during the past year was the deduction of the three-dimensional structure of the narcotic, cocaine.

Significance to NIAMD Research: The fore-going finding constituted the correction of a solution to this structural problem proposed about a year earlier by a foreign investigator, permitted the correction of structures assigned to related compounds, demonstrated the applicability of certain recently developed stereochemical principles to problems of constitution in organic chemistry, and provided a convenient means of converting cocaine into derivatives of pseudococaine.

.P.C. - 2
ecember 1954

Analysis of NIH Program Activities

Budget Analysis Sheet

0. NIAMD-62119-49
SERIAL NUMBER

1. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	9,000	1		1	1		1	
FY 1956	9,000	1		1	1		1	

2. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

3. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

None

4. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

None

.P.C. - 3

Analysis of NIH PROGRAM ACTIVITIES

Honors, Awards, and Publications Sheet

5. NIAMD - 62119-49
SERIAL NUMBER

5. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

The three-dimensional Structure of the cocaines. Part I. Cocaine and Pseudococaine," Journal of the American Chemical Society, 76: 2855-2862, 1954

1. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

.P.C. - 1
ecember 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Analgesics
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62119-50
SERIAL NUMBER

Studies in the Synthesis of Chemical Compounds of Possible Chemotherapeutic Interest.
PROJECT TITLE

T.D. Perrine
PRINCIPAL INVESTIGATOR

None
OTHER INVESTIGATORS

PROJECT DESCRIPTION:

Objective: The object is to develop methods of synthesis for certain chemical systems, to develop methods for the purification and isolation of such compounds, and to prepare certain substances for physiological testing.

Methods Employed: Studies are under way to develop the synthesis of 4-Phenylquinuclidine and of Homomorphine. Both of these compounds are desired for physiological testing. I am also attempting to find correlation of structure with absorption spectra of analgesic type compounds.

Proposed Course of Project: These studies will be continued until definitive results are obtained.

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December 1954 Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62119-50
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	9,400	1		1	1		1	
FY 1956	9,400	1		1	1		1	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANITIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62119-50
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Perrine, T.D. and May, E.L. "Synthesis of 6-Dimethylamino-4,4-diphenylheptane." J. Org. Chem. 19: 773, (1954)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Analgesics
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62119-51
SERIAL NUMBER

6. Analgesics Based on Iminoethanonaphthalenones and Aminooctahydrophenanthrenes
PROJECT TITLE

7. James G. Murphy
PRINCIPAL INVESTIGATOR

8. Everette L. May
OTHER INVESTIGATOR

9. PROJECT DESCRIPTION:

Objective: Iminoethanonaphthalenones - The objective of this work has been the preparation of substances of type I (2,5-Dimethyl-11-hydroxy- or methoxy-9-oxo-6:7-benzmorphan) A five step synthesis (respectable yields at every step) led to substance II (2,5-Dimethyl-9-oxo-11-methoxy-6:7-benzmorphan methobromide) The next step, pyrolysis of II to I (where R= Me), proved to be not a simple operation. More than one product is formed. One of these appears to be III (3,4-dihydro-1-(2-dimethylaminoethyl)-1-methyl-2(1H) Naphtholenone. Although I has not yet been isolated, it is estimated that this problem will yield to further effort.

Aminooctahydrophenanthrenes- The objective of this work has been the preparation of amines based on the ring system of sic-as-octahydrophenanthrene, IV, for evaluation as analgesic agents.

This structure appeared worthy of consideration because it is a replica of the hydrogenated phenanthrene ring system of morphine, the aromatic ring being in proper position and rings 2 and 3 being cis-locked as in the natural alkaloid. The ketone, V,(9-oxo-cis-as-octobydrophenanthrene) 2-phenylcyclohexanone in a three step synthesis A Mannich reaction on this gave the aminophenanthrone VI (10-Dimethylominomethyl-9-oxo-cis-as-octobydroplenanthrene).

The derived alcohol and acetylated compound, VII (10-Dimethylamino-methyl-9-hydroxy-cis-as-octabydro-phenanthrene) and VIII, (9-Ocetoxy-10-dimethyl-aminomethyl-cis-as-Octahydrophenanthrene)

VI, VII, and VIII have been submitted for evaluation as analgesic agents, of which the first two are now know to be active substances.

The activity found in this series is all the more interesting

Project Description Sheet Continued

in that:

1. The compounds do not have a quaternary carbon.
2. The nitrogen is separated by one carbon atom from the position it would have to occupy to be a more exact morphine analog.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62119-51
SERIAL NUMBER

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	8,000	1		1	1		1	
FY 1956	8,000	1		1	1		1	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956; IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62119-51
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Structures Related to Morphine. I. 2-(2-Dimethylamonoethyl)-2-Phenylcyclohexanone and Derivatives. J.G. Murpgy and E.L. May, *J. Org. Chem.*, *19*, 615-17 (1954).

Structures Related to Morphine. II. An Isomer of N-Methylmorphinan. E.L. May and J.G. Murphy, *J. Org. Chem.*, *19*, 613-22 (1954).

Structures Related to Morphine. III. E.L. May and J.G. Murphy (in press).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

.P.C. - 1
ecember 1954

Analysis of NIH Program Activities

Project Description Sheet

National Institute of Arthritis and Metabolic Diseases
INSTITUTE

Chemistry
LABORATORY

3. Steroid
SECTION

Bethesda
LOCATION

5. NIAMD - 62120-52
SERIAL NUMBER

The Spectral Characterization of Benzenoid Systems Derivable from $\Delta^{5,7}$-Steroids
PROJECT TITLE

Irving Scheer and William R. Nes
PRINCIPAL INVESTIGATORS

Ph. B. Smeltzer
OTHER INVESTIGATOR

PROJECT DESCRIPTION:

Methods Employed: The neosteroids and the anthrasteroids which possess, respectively, a tetrasubstituted benzenoid ring with angular annulation and a pentasubstituted benzenoid ring with linear annulation have been characterized by their absorption in the spectral regions from 220-400 mu, 1630-1565 cm^{-1}, and 900-720 cm^{-1}. Differentiation of the two classes of compounds is possible in either the infrared or ultraviolet region. The spectra of some related aromatic compounds are discussed in this connection.

Significance to NIAMD Research: This study is an extension of the efforts in this section of characterization and identification (quantitative determination) of steroids which may eventually bring about time and labor saving short cuts in analytical procedures.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62120-52
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	9,400	5/6	½	1 1/3	5/6	½	1 1/3	
FY 1956	9,400	5/6	½	1 1/3	5/6	½	1 1/3	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954 Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62120-52
SERIAL NUMBER

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

"Detection of Steroidal Pseudosapogenins by Infrared Spectroscopy", by A.L. Hayden, Ph. B. Smeltzer and I. Scheer, Anal. Chem. 26, 550 (1954).

"The Spectral Characterization of Benzenoid Systems Derivable from ^{5,7} Steroids", by Irving Scheer, William R. Nes and Phyllis B. Smeltzer, J. Am. Chem. Soc., 77, 0000 (1955).

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Steroids
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62120-53
SERIAL NUMBER

6. Complete Structural Elucidation of Tomatidine and Solasodine
PROJECT TITLE

7. Yoshio Sato
PRINCIPAL INVESTIGATOR

8. H.G. Latham, Jr.
OTHER INVESTIGATOR

9. PROJECT DESCRIPTION

Methods Employed: Tomatidine has been reduced to two different dihydro derivatives. The latter have been transformed by chromic acid oxidation and subsequent reduction to solanidine, a new epimeric (presumable at C-22) isosolanidine. A third isomer (epimeric at C-25) has been obtained in an analogous manner from tetrahydrosolasodine, thur, establishing the structural and steric relationship of these types of alkaloids.

Studies are under way to elucidate the structure of the nitrogen free compounds obtained by acid treatment of the N-nitroso derivatives of tomatidine and solasodine.

A natural by-product obtained in the isolation of solasodine (from the Indian solanum Xanthocarpum) called solanocarpone is being investigated.

Significance to NIAMD Research: A) Theoretical. The structural elucidation of an important group of steroidal alkaloids. These aspects are closely related to the analogous ones in the project on "Steroidal Sapogenins".

B) Practical. The plants producing tomatidine and solasodine may be possibly developed as an industrial crop and thus, become potential sources for the production of steroidal hormones, including cortisone.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62120-53
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	18,300	1	1½	2½	1	1½	2½	
FY 1956	18,300	1	1½	2½	1	1½	2½	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

3. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO. (S)

None

4. IF THIS PROJECT RESEMBLES, COMPLEMENTS OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62120-53
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Steroids
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62120-54
SERIAL NUMBER

6. Analysis of Individual Corticoids
PROJECT TITLE

7. Erich Heftmann
PRINCIPAL INVESTIGATOR

8. D.F. Johnson and A.L. Hayden
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Methods Employed: a. The method of Heftmann and Johnson for the determination of individual corticoids (see publication No. 2) is being applied to various urines (normal male, normal female, pregnancy urine, and urine from patients treated with steroidal hormones). The method is checked by recovery experiment.
b. The above method has been applied to beef adrenal extract, and individual compounds have been identified and quantitaively determined (dehydrocorticosterone, corticosterone, cortisone, dehydrocortisone, Reichstein compound D and V).

Significance to NIAMD Research: A relizble analytical procedure for the determination of the individual corticoids has been attempted, and never achieved completely by numerous laboratories in this country and abroad. Only analytical figures for the individual corticoids allow to draw conclusions as to metabolic pathways of the cortical hormones, and thus, correct interpretation of the nature and the fate of the steroidal hormones and their products of transformation and degradation in the healthy and sick organism. It is hoped that these analytical procedures will be very instrumental in the understanding of such diseases which obviously involve deviations of the normal steroidal metabolism. Example given is rheumatoid arthritis.

Budget Data Sheet

10. NIAMD - 62120-54
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	13,900	1½	½	2	1½	½	2	
FY 1956	13,900	1½	½	2	1½	½	2	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) WITHIN NIH)

None

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

5. NIAMD - 62120-54
SERIAL NUMBER

6. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

"Identification of Cardiac Glycosides and Aglycones in Strophanthus Seeds by Paper Chromatography" by E. Heftmann, P.J. Berner, Jr., A.L. Hayden, H. K. Miller and E. Mosettig, Arch. Biochem. and Biophys. 51, 329 (1954).

"Determination of Adrenocortical Steroids in Mixtures" by E. Heftmann and D.F. Johnson, Anal. Chem. 26, 519 (1954).

7. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Steroids
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62120-55
SERIAL NUMBER

6. The Synthesis of Corticoid Glucuronides
PROJECT TITLE

7. Edward M. Fry
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The synthesis of "the glucuronides" i.e., the β-D-glucopyranuronic acids of corticoids (desoxycorticosterone, cortisone, hydrocortisone and others).

There is sufficient evidence that corticoids are present in urine at least, in form of gluconides (particularly on account of hydrolysis with β-glucuronidase). A synthesis would establish this point beyond doubt and would, moreover, provide materials to study the various hydrolytic procedures employed more or less hapharzardly at present in the analysis of corticoids.

The synthesis of glucurono-1,6-lactone was undertaken for the purpose of seeing whether or not this compound is a suitable intermediate for the preparation of the alkyl β-D-glucopyranuronic acids needed in model studies.

Significance to NIAMD Research: Direct connection with the project on "Analysis of individual corticoids", Heftmann.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62120-55
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	11,700	1	½	1½	1	½	1½	
FY 1956	11,700	1	½	1½	1	½	1½	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO. (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIMD - 62120-55
SERIAL NUMBER
6

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Steroids
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62120-56
SERIAL NUMBER

6. The Study of Fecal Steroids
PROJECT TITLE

7. Erich Heftmann
PRINCIPAL INVESTIGATOR

8. P.J. Berner, Jr.; A.L. Hayden; D.F. Johnson
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Methods Employed: A 2 kg. sample of normal male feces was worked up completely, and various ketosteroids were demonstrated but not unequivocally identified by paper chromatography. This project is being continued with the cooperation of the Section on Fractionation and Isolation (Dr. J.C. Keresztesy) : 50 kg. of stool are being collected and extracted.

Significance to NIAMD Research: There has nowhere and at no time been made a thorough and systematic study of fecal contents, in particular not of steroidal products. This latter class of fecal products appears to be of outstanding interest since it may lead to the understanding of the complex ways of steroidal metabolism.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62120-56
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	22,700	2	1½	3½	2	1½	3½	
FY 1956	22,700	2	1½	3½	2	1½	3½	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

Section on Fractionation and Isolation, Laboratory of Biochemistry and Nutrition SERIAL NUMBER-NIAMD- 62116-28

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

R.P.C. - C
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62120-56
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolis Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Steroids
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62120-57
SERIAL NUMBER

6. The Structure of the Aglycone of Stevioside
PROJECT TITLE

Erich Mosettig and William R. Nee
PRINCIPAL INVESTIGATORS

None
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Methods Employed: "Steviol" and "isosteviol" ($C_{20}H_{30}O_3$) obtained by enzymatic and acid hydrolysis respectively of stevioside, the principal constituent of Stevia rebaudiana Bertoni (Bridel and Lavieille, 1931) were shown to be an unsaturated hydroxy acid (non-enolic, renamed dehydrohydroxy stevic acid), and a saturated keto acid respectively, (renamed keto isostevic acid), by characterizing the functional groups chemically and spectroscopically. Particularly by the dehydrogenation of isosteviol to pimanthrene and by the spectroscopic comparison (U.V. and I.R.) of steviol and phyllocladene one arrives for the aglycones at formulae of diterpenoid acids containing the skeleton of a perhydrophenanthrene with a cyclopentane ring attached to C-2 and to C-11.

Significance to NIAMD Research: The significance is primarily theoretical since so far no glycoside of a diterpenoid acid has been found in nature. An outstanding novelty is the tremendous sweetening power of the triglucoside of this diterpenoid acid and the nearly complete physiological inertness of the latter.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	9,400	2/3	½	1 1/6	2/3	½	1 1/6	
FY 1956	9,400	2/3	½	1 1/6	2/3	½	1 1/6	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO (S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62120-57
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FORM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Steroids
SECTION

4. Bethesda
LOCATION

5. NIAMD- 62120-59
SERIAL NUMBER

6. Elucidation of the Stereochemistry of the Spiroketal Side Chain of Steroidal Sapogenins.
PROJECT TITLE

7. Irving Scheer and Erich Mosettig
PRINCIPAL INVESTIGATORS

8. R.B. Kostic
OTHER INVESTIGATOR

9. PROJECT DESCRIPTION

Objectives: Recent studies (Scheer, Kostic, Mosettig) have established the isomerism at C-25 in steroidal sapogenins. A possibility ot prove rigidly the existence or non-existence of a (simultaneous) epimerism at C-22 offered itself through the recently discovered (Prof. Spring in Manchester, England), and biogenetically curious spaogenins of the ox-bile, the cholegenins. In a cooperative project with Merck and Co. and the Eastern Research Laboratory of the Department of Agriculture, we are first attempting to confirm the proposed structure of the cholegenins, and then transform them into the desired C-27 desmethyl sapogenins (eliminating asymmetry at C-25).

In estension of the studies of the C-25 isomerism the hitherto unknown and inaccessible 16-hydroxycoprostane and 16-hydroxycholestane were obtained in a desoxylation process starting from the 3-tosyl-26-desoxytetrahydro-sarsasapogenin (or -smilagenin) and the corresponding tigogenin derivative respectively. The very rare coprostane was obtained in excellent yields by a similar prodedure from the 3,16,26-trimesylate of tetrahydro-sarsasapogenin (or -smilagenin).

Significance to NIAMD Research: a. Theoretical. The above studies have procured substances which have been hitherto unavailable, and are of great importance in respect to spectroscopic studies and possibly as metabolic intermediates (16-hydroxy). Furthermore, in these studies the entirely unorthodox situation has been discovered, that compounds that have identical melting points give no mixture-melting point desressions, have practically identical rotations, and have identical infrared spectrs, may be different.

b. Practical. Steroidal sapogenins are potential precursors of the synthesis of steroidal hormones, including cortisone. The introduction of plants containing the analogous sapogenins, as an industrial corp is being undertaken by the Department of Agriculture.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62120-59
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

"The C-25 Isomerism of Smilagenin and Sarsasapogenin", by I. Scheer, R.B. Kostic and E. Mosettig, in press, J.A.C.S. 77, pp.... (Feb. 1955)

"Coprostane, Cholestane, and their 16- -Hydroxy Derivatives from Steroidal Sapogenins", by I.Scheer and E. Mosettig, in press, J.A.C.S. 77, pp.... (1955)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

National Institute of Arthritis and Metabolic Diseases
INSTITUTE

Pathology and Histochemistry
LABORATORY

3. Histochemistry
SECTION

Bethesda
LOCATION

5. NIAMD-62121-60
SERIAL NUMBER

Development and exploration of histochemical reactions in tissues
PROJECT TITLE

R. D. Lillie
PRINCIPAL INVESTIGATOR

J. B. Longley, R. C. Bahn
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Objectives: To further correlate chemical and morphologic structure of normal and diseased tissues by devising or adapting chemical reactions to histologic study and to explore and interpret existing chemical and empirical methods.

Histochemical studies of normal and pathological pigments clearly indicate that nerve cell melanin is chemically distinct and probably functionally different from meningeal, ocular, cutaneous and tumor melanins. Chemical distinctions are also appearing among the lipofuscin pigments, indicating diversity of chemical origin and significance and perhaps metabolic function of these bodies.

The presence of distinct enterochromaffin substances in different mammalian species appears to be demonstrated and is now under exploration.

These studies entailed the exploration and introduction into histologic technic of ellulose caprate as a more suitable resinous mounting medium for unstained sections.

Studies of histochemical enzyme localizations in the renal tubule indicate a diversity of function as well as morphology in the several segments of the nephron. This study has involved devising of new and more rapid reconstruction technics to permit precise localization in the various parts of the renal tubule.

The histochemical significance of the hitherto purely empirical hematoxylin methods is under study and it appears that neither phosphoric acid moieties nor desoxyribose aldehyde are responsible

PROJECT DESCRIPTION - Continued

for the reaction. A number of other polyphenols can be substituted in some of the reactions. Skin gives a polyphenol(ase) reaction in keratohyaline and trichohyaline, distinct from the dopa-tyrosin-ase reaction, which may account for some of the confusion in the litera literature.

Localization methods for tyrosine and its iodinated derivatives are under study with some preliminary data indicating the possibility of a successful, fairly specific localization of thyroxine.

Joint studies with E. Anderson's group on metabolic changes in ACTH producing tumors are affording opportunity for histochemical as well as chemical characterization of this hormone. Histochemical studies with R. M. Bates have led to the characterization of "pigeon milk".

Significance to NIAMD Research: As new methodology is devised, and the meanings of older methods are made apparent our general understanding of the evolution of disease processes from a better correlated morphologic and chemical viewpoint, will improve.

The improvement in understanding of disease processes increases their susceptibility to therapeutic attack.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

NO. NIAMD-62121-60
SERIAL NUMBER

1. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	53,100	5	4	9	4 1/3	4	8 1/3	
FY 1956	60,100	5	4	9	5	4	9	

2. BUDGET ACTIVITY:

RESEARCH - ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

3. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

Section on Endocrinology, LBN, NIAMD- 62115-17
Pathologic Anatomy Department, CC

4. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

(Fullmer, Burstone) NIDR-

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD-62121-60
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Bangle, R. Jr., and Alford, W. C.: The chemical basis of the periodic acid Schiff reaction of collagen fibers with reference to periodate consumption by collagen and by insulin. J. Histochem. & Cytochem. 2: 62-76, 1954.

Emmart, E. W., and Longley, J. B.: The reactivation of heat-inactivated hyaluronidase. J. Gen. Physiol. 37: 361-371, 1954

Bangle, R. Jr.; The peracetic acid-Schiff stain. Am. J. Clin. Path. 24 179-185, 1954.

Fisher, E. R., and Lillie, R. D.: The effect of methylation on basophilia. J. Histochem. & Cytochem. 2: 81-87, 1954.

Lillie, R. D., Bangle, R., and Fisher, E. R.: Metachromatic basophilia of keratin after oxidation-cleavage of disulfide bonds. J. Histochem. & Cytochem. 2: 95-102, 1954.

Lillie, R. D.: Argentaffin and Schiff reactions after periodic acid oxidation and aldehyde blocking reactions. J. Histochem. & Cytochem. 2: 127-136, 1954.

Bangle, R., Jr.: Gomori's paraldehyde-fuchsin stain 1. physico-chemical and staining properties of the dye. J. Histochem. & Cytochem. 2: 291-299, 1954.

Lillie, R. D., and Bangle, R., Jr.: The peracetic acid Schiff reaction of hair cortex. J. Histochem. & Cytochem. 2: 300-311, 1954.

Lillie, R. D.: Spurious publication dates. Science. 120: 7A, 1954.

Haymaker, W., Girdany, B. R., Stephens, J., Lillie, R.D., Fetterman, G.H.: Cerebral involvement with advanced periventricular calcification in generalized cytomegalic inclusion disease in the newborn. J. Neuropath. 13: 562-585, 1954.

Bahn, R. C.: Recent progress in hormone research. Science. 120: 744, 1954.

Longley, J. B., and Fisher, E. R.: Alkaline phosphatase and the periodic acid Schiff reaction in the proximal tubule of the vertebrate kidney. A study in segmental differentiation. Anat. Rec. 120: 1-17, 1954.

Lillie, R.D. and Henson, J.P. Greco: Xylene-cellulose caprate as a histologic mounting medium of low refractive index. Stain Technol. (In press)

16. PUBLICATIONS - Continued

Longley, J. B., and Fisher, E. R.: A histochemical basis for changes in renal tubular function in young mice. J. Cell. Comp. Physiol. (In press)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. -1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases

2. Pathology and Histochemistry
LABORATORY

3. Pathologic Anatomy
SECTION

4. Bethesda
LOCATION

5. NIAMD-62122-61
SERIAL NUMBER

6. PROJECT TITLE:

a. Study of the possible pathologic expression of immunity or hypersensitivity in experimental schistosomiasis.

b. Renal lesions induced by spermine and related substances.

c. Human pathology; diagnostic - research.

d. Pathologic studies of endocrine glands. (Completed in fiscal year 1954).

. L. L. Ashburn
PRINCIPAL INVESTIGATOR

. Gert Laquer
OTHER INVESTIGATORS

. PROJECT DESCRIPTION:

a. Immunity and hypersensitivity in schistosomiasis.

Objective: To determine whether or not immunity or hypersensitivity develops in experimental schistosomiasis.

Methods Employed: Exposure of mice to cercariae. After varying intervals mice are treated to kill the schistosomes. This exposure-treatment schedule is repeated a varying number of times in different groups of mice. In addition to clinical evaluation, pathologic reactionsto worms and ova will be evaluated in relation to schedule.

Major Findings: Data being evaluated at present.

Significance to NIAMD Research: There is disagreement as to the proper "dose" schedule in chemical treatment of this disease; some therapists even claiming that treatment does more harm than good. Data on possible immune-hypersensitivity mechanism would be helpful in rationalizing therapy.

Proposed Course of Project: Dependent on results of this preliminary study.

. PROJECT DESCRIPTION: - Continued

b. Renal lesions induced by spermine and related substances.

Objective: To determine whether or not the administered spermine or a metabolic product is responsible for renal lesions.

Methods Employed: Administration of chemical by routes primarily by-passing organs probably involved in metabolism; also administering "degraded" product.

Major Findings: None - methods still being developed.

Significance to NIAMD Research: Spermine is normally present in certain human tissues. A knowledge of the possible effect of this substance and its metabolic products on the kidney would seem of particular importance in renal disease.

Proposed Course of Project: Refinement of methods (other routes of administration, etc.) to elucidate effects of metabolic products of spermine.

c. Human pathology - diagnostic; research.

Various members of this and other sections of the Laboratory of Pathology and Histochemistry participate in the study of human tissues received from various Federal Hospitals. Although a diagnostic service is rendered, the material is used for various research purposes by many members of the Laboratory. This includes cooperation in Veneral Disease Research Program--untreated syphilis study.

.P.C. - 2
ecember 1954

Analysis of NIH Program Activities

Budget Data Sheet

.0. NIAMD-62122-61
SERIAL NUMBER

1. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	10,400	½	1	1½	½	5/6	1 1/3	
FY 1956	10,400	½	1	1½	1½	5/6	1 1/3	

2. BUDGET ACTIVITY:

RESEARCH /X/ ADMINISTRATION / /

REVIEW & APPROVAL / / TECHNICAL ASSISTANCE / /

. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

Laboratory of Tropical Diseases, NMI
Section on Pharmacology, LPT, NIAMD-62124-

. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

a. Project on schistosomiasis is a cooperative one with Dr. Luttermoser of National Microbiological Institute.

b. The principal investigators in this spermine project are Drs. Rosenthal and Celia Tabor.

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

5. NIAMD-62122-61
SERIAL NUMBER

6. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Fisher, E. R., and Rosenthal, S. M.: Pathology and pathogenesis of spermine-induced renal disease. Arch. Path. 57: 244-253, March 1954.

Fisher, E. R., and Fisher, B. : Glomerular lipoidosis in the dog. Am. J. Vet. Res. 15: 285-286, 1954.

David, J. O., Howell, D. S., Laqueur, G. L., and Peirce II. E.C.: Renal hemodynamic function, electrolyte metabolism and water exchange in adrenalectomized-hypophysectomized dogs. Am. J. Physiol. 176: 411-418, 1954.

Bangle, R. Jr., and Becker, E. B.: Giant hypertrophy of the jejunal circular rugae associated with recurrent intussusception. Am. J. Path. 30: 787-797, 1954.

The influence of the central nervous system on metabolism and endocrine activity as based on transections of the brain stem in dogs. Evelyn Anderson, Kathryn Knowlton, William T. Spence, S. M. McCann, Gert L. Laqueur, David McK. Rioch, and Webb Haymaker. (Accepted for publication by Acta Neurovegetativa, Vienne).

Neurosecretory pathways between the hypothalamic paraventricular neucleus and the neurohypophysis. (Accepted for publication in Journal of Comparative Neurology. G. L. Laqueur).

7. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

C. - 1

Analysis of NIH Program Activities

Project Description Sheet

NIAMD
STITUTE

2. PATHOLOGY AND HISTOCHEMISTRY LABORATORY

thologic Anatomy
CTION

4.
LOCATION (IF OTHER THAN BETHESDA

5. NIAMD-62122-62
SERIAL NO.

oject A: High Altitude; Project B: Production of Experimental Bacterial Endocarditis
OJECT TITLE

d Chronic Valvular Deformities; Project C: Dietary Calcification in Mice;

oject D: Pathology of Malaria in Animals; Project E: Toxicity of Iodides and Iodates

B Highman
INCIPAL INVESTIGATOR

ER INVESTIGATORS

JECT DESCRIPTION:

Project A - High Altitude

jectives: To study effects of discontinuous exposure to simulated high altitude on various species of warm and cold blooded animals.

hods Employed: Animals are exposed several hours daily in a low pressure chamber to a simulated altitude of 25,000 feet.

or Findings: Altitude rats develop in addition to polycythemia, marked adrenal and cardiac hypertrophy, cardiac vegetations, renal infarcts, and damage to the testes and other organs. Similar changes, varying somewhat in different species and strains of animals, were noted in current studies.

nificance: Our findings may be of significance to those concerned with aviation medicine, health of high altitude inhabitants, and laboratory investigation of cardiorenal, endocrine and other metabolic disorders.

posed Course of Project: Dogs exposed to high altitude will be used in study of experimental endocarditis (Proj. B).

Project B

Production of Experimental Bacterial Endocarditis and Chronic Valvular Deformities

jectives: To produce endocarditis and chronic valvular deformities, to determine factors predisposing to endocarditis, to study the development of the lesion and causes of treatment failures, and to test in vivo the effectiveness of various forms of therapy.

thods Employed: Animals acclimatized to high altitude and ground level controls were inoculated intravenously with various bacteria. Some received antibiotic therapy. Pathologic studies were made at intervals after inoculation.

jor Findings and Significance: Studies of altitude rats inoculated with viridans streptococci and treated with penicillin revealed the occasional persistence of bacteria in endothelial cells and macrophages in valvular vegetations and in necrotic and suppurative foci in the heart and kidney; this may help explain some of the causes of treatment failures and the need for prolonged treatment in human endocarditis. Some rats recovering after therapy developed valvular deformities similar to calcific aortitis and other chronic valvular deformities seen in human cardiac disorders.

Endocarditis was produced in altitude rats by intravenous injections of Hemophilus parainfluenza. Similar injections failed to produce endocarditis in ground level rats even when cortisone was administered indicating that adrenal hyperactivity is not the primary factor predisposing altitude rats to endocarditis. Evidence was found that concomitant hypoxia and polycythemia are necessary predisposing factors.

Endocarditis was readily induced in altitude rats by injecting cultures of Pneumococcus, Staphylococcus, and Hemophilus indicating that altitude rats may be useful in studying the pathogenesis and the terapy in vivo of endocarditis due to these organisms.

posed Course of Project: The susceptibility to endocarditis of dogs acclimatized to high altitude is under investigation. (If acute and chronic valvular lesions can be produced in a large animal like the dog, as they have been produced in the rat, it will greatly facilitate surgical and physiological studies on heart disease and associated metabolic disorders.)

Project C : Dietary Calcification in Mice

jectives: To determine factors causing calcified lesions in heart, muscle, arteries and lungs of C3H mice fed a purified low protein diet.

hods Employed: Various supplements are added to diet and resultant change in incidence and degree of calcification is determined histologically.

or Findings: Calcification is greatly lessened by increasing protein and by certain supplements.

ignificance: May shed light on pathogenesis of certain forms of human arteriosclerosis and on possible unknown nutritional requirements.

roposed Course of Project: Further modifications of diet as indicated by promising leads.

Project D: Pathology of Malaria in Animals

bjectives: To determine cause of death and difference in survival time in different strains of mice.

ethods Employed: Animals are studied histologically at intervals after inoculation with *Plasmodium berghei*.

ajor Findings: Pathologic changes develop more rapidly in infected Swiss mice (rarely survive 8 days) than in LAF mice (usually survive 3 weeks).

gnificance: May elucidate factors affecting resistance to malaria in man.

oposed Course of Project: Different strains of mice with different survival times after malaria inoculation will be studied histologically. In collaboration with Dr. Altland, the influence of altitude polycythemia on length of survival of mice inoculated with *P. berghei* is under investigation.

Project E: Toxicity of iodides and Iodates

jectives: To determine possible health hazards in use of iodides and iodates, particularly for prevention of colloid goiter.

thods Employed: Animals are examined histologically at various periods after administration of iodides and iodates by various routes.

jor Findings: Iodates cause damage to parietal cells of stomach and to retina.

gnificance: May be useful tool in studying pathogenesis of certain eye and stomach disorders.

posed Course of Project: Studies will be continued to determine safe therapeutic limits.

er Projects: From time to time consultation is given to or tissues are examined for various other professional workers at NIH. For example, tissues of animals infected with trypanosomiasis are being studied for Mrs. E. M. Tobie.

.C. - 2

Analysis of NIH Program Activities

Budget Data Sheet

NIAMD-62122-62
SERIAL NO.

BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
Y 1955	13,400	1	1	2	1	1/3	1 1/3	
Y 1956	13,400	1	1	2	1	1/3	1 1/3	

UDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

ENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANI-
TIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER
55 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

aboratory of Physical Biology, Section on Physiology, NIAMD
aboratory of Biochemistry and Nutrition, Section on Biochemistry and Physiology of Nutrition, NIAMD
aboratory of Infectious Diseases, National Microbiological Institute
aboratory of Tropical Diseases, " " "
aboratory of Pharmacology & Toxicology, Section on Pharmacology, NIAMD

I THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE
P LIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS),
I NTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

C. - 3

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

IAMD-62122-62
ERIAL NO.

IST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR
954:

ltland, P. D. and Highman, B. Effect of a folic acid antagonist (9-methyl PGA) upon rats exposed to high altitudes, Am. J. Physiol. 176: 1-5 (1954).

ighman, B., Altland, P. D. and Eagle, H. Experimental bacterial endocarditis in altitude rats. Development and regression of cardiac lesions, including lesions in rats treated with penicillin, A.M.A. ARCH. PATH. 58: 241-257 (1954)

ighman, B., Greenberg, J. and Coatney, G. R. Pathologic changes produced by Plasmodium berghei in resistant and non-resistant strains of mice. Rivista di parassitologia (in press).

ST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR
54:

Analysis of NIH Program Activities

Project Description Sheet

NIAMD
ISTITUTE

2. Pathology and Histochemistry
LABORATORY

Ithologic Anatomy
ECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NIAMD-62122-63
SERIAL NO.

Sudy of Mechanisms Involved in Infectious Diseases
POJECT TITLE

. M. Lerner II
PINCIPAL INVESTIGATOR

OHER INVESTIGATORS

PJECT DESCRIPTION:

Ojectives: The objective of this project is to study the course of natural and artificially induced infections, employing bacteriological, pathological, immunological, and chemical methods of investigation, in order to elucidate some of the factors influencing host-parasite relationships.

Iehods Employed:

(a Animals are injected and studied culturally and histologically to follow pathogenesis of Streptobacillus moniliformis and other infections. Specialized cultural methods are employed in cases of atypical human infections, to recover the above microorganism. Strains from human and animal infections, and from normal animals, are isolated and characterized.

(b Pathological studies are carried out in mice after induction of local injury or irritation, to determine whether detectable vascular changes in spinal cord or brain occur which influence localization of paralysis in poliomyelitis.

Mr Findings:

(a Several strains of Streptobacillus moniliformis have been isolated from a variety of atypical human infections, as well as from cases of rat-bite fever. These strains have caused acute and chronic lesions when injected into mice and monkeys, and the organisms were recovered on culture of lesions. Control animals also showed similar lesions occasionally, and cultural studies revealed an exceptionally high incidence of naturally-occurring infections with this microorganism in laboratory animals.

b) No macroscopic or microscopic changes were found in spinal cord or brain of mice injected intramuscularly with pertussis vaccine, although the incidence of paralysis in injected limb was increased when mice were infected later with poliomyelitis virus.

ignificance to NIAMD Research:

) Streptobacillus moniliformis occurs in hitherto unsuspected cases of human infection, including upper respiratory disease. The natural prevalence of this microorganism in some laboratory animals is great, which can confuse animal studies with the organism. Lesions may still be produced by injection of large doses into these animals. Great care must be exercised to exclude the possibility of natural infection with this organism.

() Absence of central nervous system damage and presence of striking local tissue changes in mice injected with pertussis vaccine suggest that the localization of paralysis might be the result of concentration of virus in a non-specific inflammatory focus. This would imply the possibility of a non-neurotropic feature of the poliomyelitis virus.

oposed Course of Project:

() Search for a suitable small experimental animal for studies with Streptobacillus moniliformis, by careful cultural screening, etc., to find an animal which does not normally carry the organism and is highly susceptible to infection with it. Study the pathogenesis of infection with this organism in such an animal, and evaluate the infectivity and virulence of the various strains which have been isolated from human and animal infections.

Continue to screen human infections culturally for this microorganism, and assess these strains in animals.

Employ immunological techniques to supplement cultural diagnostic procedures, for the identification of these strains. These will include standard serological methods, as well as opsonin measurement techniques employing phagocytosis of live and killed bacterial suspensions by blood leukocytes, according to recently developed procedures.

b Titration of poliomyelitis virus in tissues of animals infected after induction of local inflammation, in order to detect possible concentration of virus in a non-specific inflammatory focus.

Analysis of NIH Program Activities

Budget Data Sheet

IAMD-62122-63
ERIAL NO.

UDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
1955	11,700	1	½	1½	1	½	1½	
1956	11,700	1	½	1½	1	½	1½	

DGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

ENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, OVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

Laboratory of Infectious Diseases: NMI
Section on Bacterial and Mycotic Diseases
Section on Basic Studies

THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE LIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), NTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

NIAMD-62122-63

IST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

IST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 954:

December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Pathology and Histochemistry
LABORATORY

3. Pathologic Anatomy
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62122-64
SERIAL NUMBER

6. Preparation of stained tissue sections for research histopathologic study
PROJECT TITLE

7. L. L. Ashburn
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

This histopathologic preparation laboratory serves the various needs for stained tissue slides in connection with research projects being conducted in the several Institutes (excluding NCI). The data below is for the calendar year 1954.

	:Accessioned	Routine Stained Sections	Special Stained Sections	"Spare" Unstai Sections
Animal:	4050	12,906		
Surgical:	2095	5,520*	13,126	3,500
Autopsies:	89	1,805*		

*Includes slides prepared of tissues from C.C. patients (Jan.-June, 1954)

Total Slides
36,857

Budget Data Sheet

10. NIAMD - 62122-64
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	42,400	1/2	8½	9	½	7 1/3	7 5/6	
FY 1956	42,400	1/2	8½	9	½	7 1/3	7 5/6	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

Laboratory of Biologics Control, NMI -

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62122-64
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Pathology and Hitochemistry
LABORATORY

3. Comparative Pathology and Hematohogy
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62123-65
SERIAL NUMBER

6. Naturally Occurring Diseases of Laboratory Animals
PROJECT TITLE

7. Robert T. Habermann
PRINCIPAL INVESTIGATOR

8. Fletcher P. Williams, Jr.
OTHER INVESTIGATOR

9. PROJECT DESCRIPTION

Determination of the incidence and cause of the naturally occurring diseases in laboratory animals and development of methods for the control and treatment of these diseases.

Objectives: The objectives of the project are to develop robust, healthy, vigorous, "disease-free" animals for research workers at the National Institutes of Health; conduct research work spontaneous, bacterial, viral, mycotic, and parasitic diseases to enable investigators to distinguish between lesions produced experimentally from those produced by the naturally occurring diseases in the NIH animals; to develop effective methods for the control or prevention of these diseases; and to develop technics for the early recognition of an outbreak of disease in the animal colonies.

Methods Employed: The efficacy of control of parasitic diseases is determined by painting various chemical substances on the floor, cages, and racks for vermin control; by dusting of laboratory animals with insecticides; and by admixture of anthelmintics to the diet. Methods of sanitation and of care of laboratory animals and the efficacy of diagnostic methods and media re compared. Necropsy of sick, unhealthy, and aged animals is conducted with parasitological, bacteriological, and histopathological examinations to determine incidence and spread of disease.

Major Findings: The major findings of this project during the past year have been (1) the use of a saturated solution of sulfamethazine in drinking water of rabbits for the control of coccidiosis, (2) the identification of some of the common helminth eggs and protozoa of laboratory animals, and the publication of pamphlet with photomicrographs of the characteristic eggs and protozoa, and (3) the incidence and pathologic findings of histoplasmosis in 50 dogs and 50 cats.

Project Description Sheet Continued

Significance to NIAMD Research: (1) The elimination of coccidiosis in experimental rabbits makes the experimental results in liver, nutrition, and radistion studies more reliable and trustworthy. (2) The photomicrographs of helminths and protozoa makes the identification of the common helminths and protozoa infestations of laboratory animals quick and easy. (3) The minor importance of dogs and cats in the transmission of histoplasmosis to man and animals has been reported.

Proposed Course of Project: A considerable portion of the next calendar year will be devoted to the control, treatment, and elimination of diseases from the laboratory animals in the NIH animal colonies; to determine incidence of Leptospira spp. in the laboratory animals; and to determine the incidence of mycotic diseases in the laboratory animals.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62123-65
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	29.500	2	2½	4½	2	2½	4½	
FY 1956	29.500	2	2½	4½	2	2½	4½	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH : (BY SERIAL NO.(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62123-65

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FORM THIS PROJECT DURING CALENDAR YEAR 1954:

Rowley, Donald A., Robert T. Habermann, and Chester W. Emmons: Histoplasmosis: Pathologic Studies of Fifty Cats and Fifty Dogs from Loudoun County, Virginia. J. Inf. Dis., 95, 98-103, July-August 1954.

Menges, Robert W. and Robert T. Habermann: Isolation of *Haplosporangium parvum* from Soil and Results of Experimental Inoculations. Am. J. Hyg., 60:2, 106-116, September 1954.

Menges, Robert W., Michael L. Furcolow, and Robert T. Habermann: An Outbreak of Histoplasmosis Involving Animals and Man. Am. J. Vet. Res., XV:57, 520-524, October 1954.

Habermann, Robert T., Fletcher P. Williams, Jr., and Willard H. Eyestone: Spontaneous Hepatomas in Two Woodchucks and a Carcinoma of the Testis in a Badger. J. Am. Vet. Med. Assoc., 125:931, 295-293, October 1954.

Congdon, Charles C., Fletcher P. Williams, Jr., Robert T. Habermann, and Egon Lorenz: The Histopathology of Bacterial Infections in Irradiated Mice. J. Nat. Cancer Inst. (Egon Lorenz Memorial Issue). (In press)

Menges, Robert W., Robert T. Habermann, and Howard G. Stains: A Distemper-like Disease in Raccoons (Procyon lotor Tinneaus) from Kansas. J. Wildlife Management. (In press)

Kilham, L.R., Robert T. Habermann, and Carlton H. Herman: Jaundice and Bilirubinemia as Manifestations of Canine Distemper in Raccoons and Ferrets. J. Immunology. (In press)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Pathology and Hitochemistry
LABORATORY

3. Comparative Pathology and Hematohogy
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62123-66
SERIAL NUMBER

6. Study of Liver Cell Mitochondria in Relation to Dietary Procedures
PROJECT TITLE

7. G.L. Fite
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Study of the mitochondria of liver cells under various dietary conditions.

Objectives: To learn something of mitochondrial changes occurring in relation to variations in nutrients in the diet.

Major Findings: The degenerative changes in liver cells in rats on suitable diets are the earliest recognizable alterations in the liver cell and degenerative changes in mitochondria.

Significance to NIAMD Research: A little known field of investigation of considerable promise.

Proposed Course of Project: An elaborate effort, by histologic means, to identtify sizes, shapes, numbers and forms of mitochondria as related to dietary variants such as cystine, vitamin E, lipids, toxic agents etc.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62123-66
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	21,100	1	½	1½	1	½	1½	
FY 1956	21,100	1	½	1½	1	½	1½	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

Section on Biochemistry and Physiology of Nutrition, LBN NIAMD - 62113-15

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH : (BY SERIAL NO. (S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62123-66
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Fite, G.L. : The Pathology of Dietary Liver Necrosis. Annals N.Y. Acad. Sci., 57, 331-8 (1954)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Pathology and Hitochemistry
LABORATORY

3. Comparative Pathology and Hematohogy
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62123-67
SERIAL NUMBER

6. Studies on Regulation of Hemopoiesis
PROJECT TITLE

7. George Brecher and Frederick Stohlman, Jr.
PRINCIPAL INVESTIGATORS

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Transfusion of separated platelets and white blood cells as replacement therapy in aplastic anemia.

Objectives: Identification and characterization of substances capable of stimulating erythropoiesis.

Methods Employed: Bone marrow aplasia is induced by irradiation. Viable platelets and white blood cells are separated from freshly shed god blood by methods developed in this laboratory and concentrated suspensions transfused into compatible recipient dogs. Measurement of erythropoiesis involves measurement of radio-iron incorporation into red cells, radio-iron clearance, survival studies of red blood cells as well as the study of stiumlators and inhibitors of erythropoiesis.

Major Findings: (1) In addition to actual blood loss secondary to thrombocytopenia, anemia in platelet deficient dogs is aggravated by continued excape of red cells from small vessels. The red cells are absorbed by lymphatics and returned to the general circulation but their life span is reduced, presumable due to damage during their extravascular cycle. This potential cause of shortened red cell survival has not been previously realized and is probably operative in severe thrombocytopenis of any type. (2) While measuring red cell survival by tagging cells with radiochromium it was found that changing chromium lossi s very sensitive indicator of red cell damage.

(3) Severely depressed erythropoiesis of irradiated rats could be returned to normal by post-radiation bleeding or administration of para-aminopropiophenone (PAPP). The use of the irradiated animals may be helpful, since responsiveness to the erythropoietic stimulus may be of critical importance in trying to assess stimulators and inhibitors.

Significance to NIAMD Research: Anemia is a common complication of arthritis and may be refractory to treatment. A better understanding of regulation of erythropoiesis should result eventually in imporved therapy.

Proposed Course of Project: Transfusion of plasma and plasma fraction from animals with peak erythropoiesis to recipients capable of responding to humoral stimulation will be used in an attempt to characterize the postulated factors.

R.P.C. - 2
December 1954

Analysis of NIH Program Activites

Budget Data Sheet

10. NIAMD - 62123-67
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	20,600	1	2 1/3	3 1/3	1	2 1/3	3 1/3	
FY 1956	20,600	1	2 1/3	3 1/3	1	2 1/3	3 1/3	

12. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	TECHNICAL ASSISTANCE	☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO. (S)

Naval Medical Research Institute

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62123-67
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Brecher, G., F. Stohlman, Jr., and E.P. Cronkite: Shortened Red Cell Survival in Experimental Thrombocytopenia Induced by Iorizing Radiation. Revue b'Hematologie.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

National Institute of Arthritis and Metabolic Diseases
INSTITUTE

Pathology and Histochemistry
LABORATORY

3. Comparative Pathology and Hematology
SECTION

Bethesda
LOCATION

5. NIAMD-62123-68
SERIAL NUMBER

Comparative pathology of virus diseases
PROJECT TITLE

Dr. Ladd N. Loomis
PRINCIPAL INVESTIGATOR

None
OTHER INVESTIGATORS

PROJECT DESCRIPTION

a. A study of the pathology of central nervous system virus infections

Objective: On a cooperative diagnostic basis the study of various central nervous system disorders for evaluation as to whether it is of a virus origin or not. Some animals that show clinical signs of a CNS disorder do not always have a diagnosable neurotrophic virus lesion.

Methods Employed: Standard pathological methods

b. Cooperative study of a technic of virus purification (Newcastle Disease virus)

Objectives: To see if the use of cellulose filtration combined with an antigen antibody complex will result in virus purification after ultracentrifugation.

Methods Employed: Ultracentrifugation of allantoic fluid Newcastle Disease preparations.

Filtration using powdered cellulose columns coated with anti-allantoic fluid protein rabbit sera and re-evaluating the purified virus by means of LD-50 and virus hemagglutination tests.

c. Monkey safety tests of the Salk polio vaccine

Objectives: Examination of brain and spinal cord tissue sections from inoculated Rhesus and Cynomologous monkeys for evidence of live virus in the Salk polio vaccine.

9. PROJECT DESCRIPTION - Continued

d. A study of the pathogenesis of Rous sarcoma and a study of the skeletal muscle lesion

Objectives: A study of early lesions of tumor genesis in Rous infected chickens beginning from 12 hours to 20 days.

Methods Employed: Using standard preparations and special stains for cell differentiation of, and mucin production by, the tumor.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD-62123-68
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	11,300	1	1/3	1 1/3	1	1/3	1 1/3	
FY 1956	11,300	1	1/3	1 1/3	1	1/3	1 1/3	

2. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

3. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

Section on Physical Biochemistry, LPB, NIAMD-62130-
Section on Pathologic Anatomy, LPH, NIAMD-62122-
Section on Carbohydrates, LC, NIAMD-62118

4. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD-62123-68
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

7. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Pathology and Hitochemistry
LABORATORY

3. Comparative Pathology and Hematohogy
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62123-69
SERIAL NUMBER

6. Degenerative Joint Disease in Small Laboratory Animals
PROJECT TITLE

7. Leon Sokoloff
PRINCIPAL INVESTIGAROR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The object of this project is to determine factors influencing development of degenerative joint diseases in small laboratory animals.

Methods Employed: Histologic, and to a lesser extent roentgenologic examination of the joints of various small animals in two categories is being made: 1. spontaneously aged and 2. experimentally altered conditions.

Major Findings: A. Because degenerative joint disease is largely a manifestatio of senescence (e.g. 18-24 months of age in rats and mice) much of the effort of the last year has been devoted to developing a colony of old animals. To date, approximately 1500 old animals comprising 13 strains of mice, 11 of rats, as well as hamsters and guinea pigs have been obtained. Approxiamtely half of these have been harvested to date. Conclusions concerning the natural history of articular degeneration are necessarily tentative at the present time. A pattern of spontaneous cystic degeneration of articular cartilage has been found in rats but this species is strikingly resistant to development of osteoarthritis unlike mice and hamsters.
B. Osteoarthritis has been found to develop in a proportion of old obese rats (Dr. Mickelsen), and rats exposed to conditions simulating high altitude (Dr. Altand). Negative results have been obtained in thyro-hypophysectomized rats (Dr. Scow), those on cirrhosis-producing diets (Dr. Daft) or those treated with Growth Hormone for 90 days.
C. A variety of undescribed spontaneous disorders of the extremities have been observed (congenital and acquired) that will be of interest

to geneticists and workers in the field of experimental arthritis. An example of the former is isolated absence of the secondary center of ossification in the capital epiphysis of the femur. Example of latter include cellulitis and actinomycosis of the paws.

Significance to NAIMD Research: Degenerative osteoarthritis is the commonest and economically most destructive form of human joint disease from the poin of view of public health. It has, with one outstanding exception, not been the subject of systemic experimental study in recent years. This reflects a popular assumption that the disorder is an inevitable manifestation of old age. Although recognized to occur in virtually all bulky mammals, rodants have been considered immune until recently. The results in the small rodents encourage the hope that prophylactic measures, if not inhibiting agents, may be devised for the human disorder.

Proposed Course of Project: 1. Distribution of degerative changes in the various species is being determined: A. to determine joints most suitable for study in this field. B. to compare effect of posture on development in these species compared to others. 2. Radiologic methods for diagonsis are being evaluated with paired histologic preparations. 3. Genetic studies are to be carried out with Dr. Jay in an attempt to produce high arthritis strains. Almost all the animals are from the inbred colony, so that their genetic background is known. 4. Histochemical studies will attempt to define similarities and differences from the human disorder. Chemical alterations in the matrix of the cartilage that allow its erosion to come about may be divulged by appropriate methods. 5. Expermental production of ostearthritis will be pursured in collaboration with: A. Dr. Mickelsen: effects of obesity of various diets, obesity plus forced exercise in rats B. Dr. Altland: high altitude exposures in hamsters. C. Independently it is planned to obscure the effects of thymectomy and salenium on the joints.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62123-69
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	18,600	1	2 1/3	3 1/3	1	2 1/3	3 1/3	
FY 1956	18,600	1	2 1/3	3 1/3	1	2 1/3	3 1/3	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVEIW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO. (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH : (BY SERIAL NO. (S) IF WITHIN NIH)

None

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62123-69
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Sokoloff, Leon (with I.O. Gleason): The Sternoclavicular Articulation in Rheumatic Diseases. Amer. J. Clin. Path., 24, 406, 1954.

Bunim, Joseph J., Leon Sokoloff, Robert R. Williams, and Roger L. Black: Rheumatoid Arthritis: A Review of Recent Advances in our Knowledge Concerning Pathology, Diagnosis, and Treatment. J. Chronic Diseases. (In press)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Pharmacology and Toxicology
LABORATORY

3. Pharmacology
SECTION

4. Bethesda
LOCATION

5. NIAMD-62124-70
SERIAL NUMBER

6. The biosynthesis of the micropolysaccharides and glucuronates; the cellular localization of hyaluronidase

7. Jack L. Strominger
PRINCIPAL INVESTIGATOR

8. E. W. Emmart
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Objectives: To elucidate the mechanism of biosynthesis of the mucopolysaccharides and glucuronates. By the use of fluorescin labeled antibody to streptococcal hyaluronidase to determine the cellular localization of this enzyme in mammalian tissues.

Major Findings: Chromatographis methods were developed for the isolation of uridine nucleotides. High concentrations were found in the hen's oviduct, and characterization of some of these compounds revealed that they were uridine pyrophosphate combined with (a) N-acetyl glucosamine and (b) N-acetyl galactosamine sulfate. Since the oviduct is important in the synthesis of glycoproteins and mucopolysaccharides, these findings suggest a biosynthetic pathway.

An enzyme was obtained from liver which oxidizes uridine diphosphate glucose to uridine diphosphate glucuronic acid, thus demonstrating the pathway of formation of the glucuronates. The enzyme has been purified 180 fold.

Using the method of labeling antibody by azolinkage to a fluorescent dye, antibody against streptococcal hyaluronidase has been produced in rabbits, and the serum labeled in this way. Equipment for microscopic demonstration is being assembled, and after injection of the antigen in mice, tissues will be treated with the fluorescent antibody, and the localization studied histologically. It was also found that hyaluronidase, inactivated by heat, becomes spontaneously reactivated on standing.

9. PROJECT DESCRIPTION - Continued

Proposed Course of Project: The resignation of Dr. Strominger to accept a Markle Fellowship prevents formulation of future plans for biochemical studies. The histochemical localization of injected hyaluronidase will be continued.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD-62124-70
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER		PROF	OTHER	TOTAL	
FY 1955	25,300	2	1½	3½	2	1½	3½	
FY 1956	25,300	2	1½	3½	2	1½	3½	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

3. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

Cole NMI - 69
Section on Histochemistry, LPH, NIAMD- 62121-60
Section on Enzymes and Cellular Biochemistry, LBN, NIAMD- 62115-24
Section on Enzymes and Cellular Biochemistry, LBN, NIAMD- 62115-26

4. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHING NIH)

None

P.C. - 3
ecember 1954

Analysis of NIH Program Activities

Honors, Awards, and Publication Sheet

NIAMD-62124-70

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Strominger, J. L., L. A. Heppel and E. Maxwell. A new mechanism for dephosphorylation of nucleoside di- and triphosphates. Arch. Biochem. and Biophysics 1954, 52, 488.

Strominger, J. L., H. J. Kalkar, J. Axelrod, and E. S. Maxwell. Enzymatic oxidation of uridine diphosphate glucose to uridine diphosphate glucuronic acid. J. Am. Chem. Soc. Dec. 20, 1954.

Strominger, J. L., and O. Lowry. Quantitative Histochemistry of Brain. IV. Lactic, malic and glutamic dehydrogenases. J. Am. Chem. Soc. (In press).

Emmart, E. W., and J. B. Longley. The reactivation of heat inactivated hyaluronidase. J. Gen. Physiol. 1954. 37, 361.

Emmart, E. W., and J. C. Keresztesy. The effect of a concentrate of nocardin on the growth of streptomycin sensitive and resistant strains of mycobacteria tuberculosis. Mycopathologia. Vol. VI No. 4, 1954

17 LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Pharmacology and Toxicology
LABORATORY

3. Pharmacology
SECTION

4. Bethesda
SECTION

5. NIAMD - 62124-71
SERIAL NUMBER

6. Metabolic Processes, Drug Action and Physical Chemistry Related to Electrolyte Distribution and Bioelectrical Phenomena as Exemplified by Nerve.
PROJECT TITLE

7. Dr. Abraham M. Shanes
PRINCIPAL INVESTIGATOR

8. Mr. Morris Berman
OTHER INVESTIGATOR

9. PROJECT DESCRIPTION

Objectives: To determine the effect of metabolic inhibition and substrates, of drugs with no demonstrable metabolic action but with a demonstrated effect on electrolyte distribution, and of alterations in the ionic milieu on the kinetics of entry and exit of sodium, chloride and potassium in nerve. The relation of these to the maintenance of cellular membrane potentials and to the production of action potentials also is to be established.

Method Employed: Desheathed sciatic nerves of the toad which our studies have demonstrated to be particularly favorable preparation , are exposed in vitro to radioisotope solutions and the kinetics of entry and exit are followed under conditions of metabolic inhibition and in the presence of substrates, drugs or modified medium. The variations of bioelectrical potentials under similar conditions can be followed with suitable electrical equipment.

Major Findings: Vertebrate nerve preparations have been found and techniques of study have been developed which permit a discrimination of ions located in the extracellular spaces from those in the axons proper. They also permit the study of the rates of entry and exit of the ions through the fiber membranes under strictly steady state conditions as well as under a variety of experimental conditions. Thus, it has been possible to show that the temperature coefficient for the emergence of sodium and chloride from the fibers is twice as great as that from the extracellular spaces. The excape of sodium is not markedly affected by oxygen lack even when combined with inhibition of glycolysis. However, return to oxygen following deprivation causes an acceleration of sodium efflux.

Project Description Sheet Continued

Single nerve fibers such as from the squid exhibit a phase which appears to be comparable to the extracellular space. In these preparations oxygen lack slowed sodium escape but accelerated potassium emergence. Cocaine slowed potassium efflux but not that of sodium.

Significance to NIAMD Research: By the demonstration of the relation of metabolic processes and their derangement to normal functioning and malfunctioning of cells as examplified by nerve (which in many respects is quite similar to other cells of the body), a basis is being laid for an understanding of the nature of disturbances associated with metabolic diseases and for the development of means of treatment. The ease with which bags of connective tissue may be obtained by desheathing nerves commends their use for study of durgs, hormones, etc. on their permeability, structural, and other characteristics.

Proposed Course of Project: Sodium, chloride and potassium radioisotopes will be employed in studying the specificity (a) of metabolic inhibition-induced by oxygen lack, glycolysis inhibition (iodoacetate poisoning), azide and dinitrophenol - (b) of drug action, as exemplified by anaesthetic agents such as cocaine and excitatory agents like veratrine alkaloids and (c) of the ionic milieu on the transfer of these ions out of and into the nerve fibers. Time and space permitting, exploratory studies will be attempted to correlate the bioelectrical phenomena of these nerves with the chemical findings.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62124-71
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	17,100	2	0	2	2	0	2	
FY 1956	17,100	2	0	2	2	0	2	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62124-71
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Shanes, A.M. "Effects of sheath removal on the sciatic of the toad, Bufomarinus" J. Cell. Comp. Physiol. 43:37, 1954.

Shanes, A.M. "Effects of temperature on potassium liberation during nerve activity". Am. J. Physiol. 177:377, 1954

Shanes, A.M. "Sodium exchange through the epineurium of the bullfrog sciatic." J. Cell. Comp. Physiol. 43:99, 1954.

Shanes, A.M. "Factors governing ion transfer in nerve." Suppl. Physiol. Rev. In press.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Dr. Shanes was selected as organizing chairman of the Symposium on "Electrolytes in Biological Systems", which met in Woods Hole, Mass. on Sept. 3, 1954 under the Society of General Physiologists.

Dr. Shanes is to be editor of a monograph on "Electrolytes in Biological Systems" to be published by the Am. Physiological Society with the support of the National Science Foundation.

R.P.C. 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Pharmacology and Toxicology
LABORATORY

3. Pharmacology
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62124-72
SERIAL NUMBER

6. The chemotherapy of mouse leprosy. Toxicology of iodates and related compoun
PROJECT TITLE

7. Y. T. Chang (fellow), W. F. von Oettingen, S.H. Webster, E.L. Jackson.
PRINCIPAL INVESTIGATORS

8. Mary E. Rice,
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The toxicology and evaluation of therapeutic effectiveness of drugs in leprosy. The toxicology of iodates as a basis for use i iodized salt to prevent goiter. The relation of isomers of thyroxin to physiological activity.

Major Findings: Methods have been devised for quantitative evaluation of drugs in leprosy, using intraperitoneally infected mice. Several compounds have been found superior to the sulfones, which at present are the basis of human therapy. The isonydrazides, streptomycin, and certain sulfones represent the order of effectiveness. Combination therapy showed an additive but not synergistic effect. Experiments indicate that prolonged therapy may result in the acquisition of tolerance by the bacteria, hitherto not established for this organism. (Chang).

The acute toxicity of the iodates causes nerbous symptoms, hematological changes and under certain conditions retinitis pigmetosa. Sublethal doses administered in the drinking water for several months have been essentially devoid of toxicity and indicate the safety of iodate for use in iodized salt. Studies on the use of organ weight - body weight ratio as an index of toxicity are being continued. (Webster)

A survey of the clinical toxicity of the antibiotics has been made to evaluate their hazards in clinical use. A book on the toxicity of the halogenated hydrocarbons has been submitted for publication. (von Oettingen)

Project Description Sheet Continued

A meta isomer of thyroxin is being prepared for testing of thyroxin activity. It may possible function as an antimetabolite to antagonize thyroxin action. Some related new iodinated tyrosine compounds were prepared in the course of this work. (Jackson)

Significance to NIAMD Research: The leprosy studies are carried out in cooperation with the Am. Leprosy Foundation (Dr. Chang is on a Fellowship from them). The results are applied to their clinical evaluation studies.

The use of iodate to iodinize salt is a problem of importance in tropical countries, where the volatile and hygroscopic properties of KI presents a difficulty.

Proposed Course of Project: Continuation of evaluation of drugs in mouse leprosy. Studies on the metabolism of acid fast organisms. Completion of the toxicological studies on iodates.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62124-72
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	38,600	2½	2	4½	2½	2	4½	
FY 1956	38,600	2½	2	4½	2½	2	4½	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

Dr. Chang (American Leprosy Foundation Fellow)

14. IF THIS PROJECTSRESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62124-72
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Sulfone therapy in mouse leprosy. Y.T. Chang, R.R. Walcott and J.A. Dowll. Med. Clinics of North America, 1954: 33, 599.

Chemotherapy of Murine leprosy. III. Comparative Activity of Nicotinamide and Pyrazinamide on Mouse Leprosy. Internat. J. of Leprosy. (In press).

IV. The effects of amithiozone, p-aminosalicylic acid, B233, 5 anti-biotics an 3 phenylthiourea compounds on mouse leprosy. Y. T. Chang. Internat. J. of Leprosy. (In press)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Pharmacology and Toxicology
LABORATORY

3. Pharmacology
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62124-73
SERIAL NUMBER

6. The physiological function, intermediary metabolism, and pathological effects of spermine and related amines.
PROJECT TITLE

7. Drs. S.M. Rosenthal, Celia W. Tabor
PRINCIPAL INVESTIGATORS

8. R.C. Greene and E.L. Jackson
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: Spermine has been found to be a potent nephrotoxic agent. Since it is widely distributed in mamallian tissues, its metabolism, function, and relation to renal disease is being studied.

Methods Employed: An amine oxidase from beef plasma which degrades spermine and spermidine has been purified 200 fold. The products of degradation are being isolated and characterized, and their toxicity determined. Attempts to find an antagonist to the nephrotoxic action are being made, using mice as the test object. Studies have been initiated upon mutant organisms and Neisseria to find bacteria that require spermine, as a tool to elucidate its physiological significance. Chromatographic methods for estimation of these amines have been developed.

Major Findings: Spermidine, putrescine and an amino aldehyde (not yet characterized) have been demonstrated as enzymatic breakdown products of spermine. Since ethylene and propylene diamine and ethylene imine also have similar nephrotoxic effects, attention is focused on an amino aldehyde or a cyclic derivative as the couse of kidney damage.

Administration of the enzyme will protect mice against one or more lethal doses of spermine.

The oxidation products of spermine have marked toxic effects on bacteria and germ cells. Thus, several species of bacteria or spermatozoa are killed by low concentrations of spermine in the presence of the enzyme. This suggests a physiological significance and also affords an additional tool for elucidating mechanism of action.

The distribution of spermine and spermidine in various tissues has been determined.

Project Description Sheet Continued

Significance to NIAMD Research: Spermine and spermidine are widely distributed in mammalian and plant tissues and no previous work has demonstrated any physiological function or relation to disease. It is believed that this work will throw light on their biochemical significnace, and that a causative relationship may be shown to some types of human renal disease.

Proposed Course of Project: (a) Further identification of the breakdown products of spermine and spermidine, and their relation to kidney damage.

(b) Further functional and pathological studies of the kidneys after administration of spermine or its breakdown products.

(c) Measurement of spermine in blood and urine after experimentally produced renal lesions.

(d) Study of the lethal effects of the breakdown products on bacteria and spermatozoa to elucidate the mechanism and to obtain an antagonist to spermine toxicity.

(e) To study the biochemical significnace of these amines by employing mutant bacteria and by isotopic labeling.

(f) An imporved method of synthesis of spermine and spermidine is in progress, which will make these compounds more available, and facilitate isotopic labeling.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62124-73
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	36,200	2½	2	4½	2¼	2	4½	
FY 1956	38,200	3	2	5	3	2	5	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

Section of Pathologic Anatomy, LPH NIAMD - 62122-61

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Acitvities

Honors, Awards, and Publications Sheet

15. NIAMD - 62124-73
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

"Pathology and Pathogenesis of Spermine Induced Renal Disease." E. R. Fisher and S. M. Rosenthal. Arch. Path. 1954: 57, 244.

"Purification of Amine Oxidase from Beef plasma". C. W. Tabor, H. Tabor, and S.M. Rosenthal, J. Biol. Chem. 1954: 203, 645.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Pharmacology and Toxicology
LABORATORY

3. Pharmacology
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62124-74
SERIAL NUMBER

6. Mechanisms and therapy of traumatic shock
PROJECT TITLE

7. Dr. R. Carl Millican and Dr. S. M. Rosenthal
PRINCIPAL INVESTIGATORS

8. Dr. Kehl Markley and Mr. E.F. Stohlman,
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: (1) Study the role of fluids, electrolytes and plasma proteins in the cause and treatment of shock. (2) Cause and therapy of late deaths in burn shock. (3) Clinical evaluation in burn shock of the effectiveness of large volumes of saline solutions.

Methods Employed: 1. Standardized traumatic shock produced in mice by application of tourniquets to hind legs or dipping animals in hot water. Mortality studies. analyses of fluid, electrolyte and colloid distribution employed to study mechanisms for effectiveness of fluid therapy in treatment of shock. Isotopically labeled plasma proteins and sodium used for distribution studies.
2. In the clinical study of burn shock plasma therapy is compared with large volumes of saline solutions on an alternate case basis. Clinical study (in cooperation iwth Research Grants Division of NIH) is in progress in Lima, Peru. Patient material consists of burn cases admitted to charity hospitals in Lima. The study induludes mortality, measurements of hemodynamic effects of therapy; sodium, potassium and fluid balance studies; rate of gastrointestinal absorption; and measurements of plasma volume after therapy.

Major Findings: 1. Demonstration of the therapeutic effectiveness of intraperitoneally administered whole blood, plasma, albumin in saline, and saline in the treatment of burn shock in mice.
2. Radioactive tracer studies indicate that, as swelling occurs, protiens of the plasma rapidly exchanges with the plasma protein accumulating in the injured area. After swelling is complete, the exchange of protein in the fluid accumulated in the injured area is greatly prolonged, indicating a sluggish pool.

3. Demonstration in mice that plasma therapy is more effective when administration is delayed until the initial swelling of injured area was complete. Saline therapy in equivalent volumes, whether administered before or after swelling was complete, was not as effective as delayed plasma administration.

4. Preliminarey evidence of the clinical efficiency of large volumes of saline in burn shock. With approximately 100 cases in each group, results to date indicate equal effectiveness of plasma therapy and saline therapy. No toxic effects form large volumes of saline therapy. No toxic effects from large volumes of saline were observed.

Significande to NIAMD Research: Knowledge of the fluid, electrolyte and colloid disturbances which occur in shock are of interest in the understanding of metabolic diseases.

Proposed Course of Project: 1. Future work will be concerned with further quantitative studies on the distribution of fluids, electrolytes and proteins in the schocked animal and with evaluation of relative efficiency of fluids administered in shock and the factors affecting their therapeutic effectiveness. Work will be continued on the cause and therapy of late deaths following extensive burns in animals and in man.

2. The clinical study, of burns in Liam, Peru has entered the second phase of the project. For the next 15 months on an alternate case bases a comparison will be made of large volumes of saline solution with plasma supplemented with sufficient saline to make the fluid and electrolyte equivalent in both groups.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIMD - 62124-74
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	45,700	3½	2	5½	3½	2	5½	
FY 1956	47,700	3½	2½	6	3½	2½	6	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

Dr. Hurtado, Lima Peru Burn Study, Instituto de Biologia y Patologia
Hospital Arzobispo - Loayza, Lima, Peru

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62124-74
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Rosenthal, S.M. and R. Carl Millican, "The role of fluids, electrolytes, and plasma protiens in experimental traumatic shock and hemorrhage". Pharm. Rev., December, 1954.

Millican, R. Carl, "S^{35}-Plasma and erythrocyte distribution in tourniquet-shocked mice". Am. J. Physiol., 179, December, 1954.

Millican, R. Carl, "Tourniquet shcok in mice. Na^{22} and S^{35}-plasma turnover in the accumulated fluid in the area of injury". Am. J. Physiology, 179, Dec. 1954.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases

2. Pharmacology & Toxicology
LABORATORY

3. Biochemical Pharmacology
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62125-75
SERIAL NUMBER

6. Elucidation of the Enzymatic Mechanisms for the Biosynthesis of Asparagine and Homoserine
PROJECT TITLE

7. Simon Black
PRINCIPAL INVESTIGATOR

8. Mrs. Nancy G. Wright
OTHER INVESTIGATOR

9. PROJECT DESCRIPTION

Objectives: A larger objective is the discovery of mechanisms of "activating" amino acids for incorporation into proteins.

Methods Employed: Cell-free enzyme extracts of plant and animal tissues and of bacteria are prepared and tested for their ability to catalyze the conversion of radioactive aspartic acid to asparagine and homoserine. Chemical tests for such conversions are also employed.

Major Findings: It has been shown for the first time, with intact plant cells, that aspartic acid is a precursor of asparagine and of homoserine. The enzyme homoserine dehydrogenase is widely distributed in plants. Extracts of spinach leaves possess a small ability to form homoserine from aspartate.

Significance to NIAMD Research: Knowledge of the intimite chemical transformations of amino acids in living cells will serve as a basis for better understanding of the nature of disease and its more intelligent treatment.

Proposed Course of Project: The work will be pursued in the present manner until the individual chemical steps involved in the transformation of aspartate to asparagine and homoserine have been established.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62125-75

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	19,000	1	1	2	1	1	2	
FY 1956	19,000	1	1	2	1	1	2	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62125-75
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Black, S. and Wright, N.G. Journal of Biological Chemistry (1955 - in press)

β-Aspartokinase and β-Aspartyl Phosphate

Aspartic β-Semialdehyde Dehydrogenase and Aspartic β-Semialdehyde

Homoserine Dehydrogenase

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Pharmacology and Toxicology
LABORATORY

3. Biochemical Pharmacology
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62125-76
SERIAL NUMBER

6. Histidine, Histamine and Related Imidazoles
PROJECT TITLE

7. Herbert Tabor
PRINCIPAL INVESTIGATOR

8. A.H. Mehler, E. Adams, O.H. Hayaishi, H. Bauer, (fellow)

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9. PROJECT DESCRIPTION

Objectives: To study the biosynthesis, intermediary metabolism, and pharmacological activity of these compounds in order to understand better their physiological and pathological role.

Major Findings: The major findings during the past year have been the demonstration that imidazoleacetic acid riboside is a major intermediate in the metabolism of histamine (Tabor, Hayaishi, Bauer). Further work has also been carried out on the nature of the intermediary steps involved in histidine metabolism. (Tabor, Mehler) The immediate precursor involved in the biosynthesis of histidine has been synthesized, and identified as histidinal (Dr. Adams.)

Significance to NIAMD Research: Histidine is an essential amino acid, and enters into many important metabolic relationships. The C-2 of the imidazole ring is important in "one-carbon metabolism", and is closely related to studies on the role of folic acid in metabolism. Changes in histidine metabolism have been described upon alterations in the hormonal pattern, particularly in rheumatoid arthritis. Histamine is powerful pharmacological agent which is normally present in tissues. It appears to be very important in gastric secretions, neurohormonal reaction to stress, certain types of neural transmission, and in allergy and anaphylaxis. Histamine appears to be very important in stimulating the adrenal anterior pituitary system. It is anticipated that further studies on its metabolic interrelationship will aid in clarifying histamine's role in these phenomena.

Project Description Sheet Continued

Proposed Course of Project: I. Histamine Metabolism

A. Nature of other urinary metabolites after administration of C^{14} histamine.
B. Enzymatic syntheses of Imidazoleacetic acid riboside
C. Enzymatic degradation of imidazoleacetic acid.
D. Physiological and pharmacological studies as indicated by the development of the project.

II. Histidine Metabolism

A. Purification of Various enzymes involved in conversion of histidine to glutamic acid. Particular emphasis will be directed towards one-carbon transfer studies.
B. Biological syntheses and degradation of carnosene, anserine, and other related imidazoles.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62125-76
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	51,800	3 1/3	2	5 1/3	3 1/3	2	5 1/3	
FY 1956	57,700	4	4	3	4	3	7	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62125-76
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Preparation of Urocanic Acid. A.H. Mehler, H. Tabor and H. Bauer. Biochemical Prepns. In press.

Preparation of Histidinol. H. Bauer, E. Adams, and H. Tabor, Biochemical Prepns. Submitted.

Isolation of Formyl-L-Glutamic Acid from the Enzymatic Degradation of L-Histidi
H. Tabor, A.H. Mehler, J. Biol. Chem. 210:No. 2, 1954.

Metabolic Studies on Histidine, Histamine and Related Imidazoles
Herbert Tabor. Pharmacological Reviews, 6: 299-343, 1954.

Enzymatic Formation of Formylaspartic Acid from Imidazoleacetic Acie
O. Hayaishi, H. Tabor and T. Hayaishi, J. Am. Chem. Soc., 76, 5570, 1954.

Synthesis of a Metabolic Product of Histidine. J.E. Seegmiller, M. Silverman, H. Tabor, A.H. Mehler, J. Am. Chem. Soc., 76: No. 23, 6205, 1954.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Pharmacology and Toxicology
LABORATORY

3. Biochemical Pharmacology
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62125-77
SERIAL NUMBER

6. Biosynthesis of Nicotinic Acid
PROJECT TITLE

7. Alan H. Mehler
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To isolate the individual steps in the sequence of reactions resulting in nicotinic acid formation, to study the properties of the enzymes involved, and to describe the intermediate metabolites.

Methods Employed: Enzymes are obtained form various sources and purified by the variety of methods currently used in this field. Chemical and physical, especially spectrophotometric, methods are used to measure enzyme activity and to identify products. Possible substrates and products are synthesized by conventional organic chemical techniques.

Major Findings: The principal finding of the past year was the demonstration of a previously unknown enzyme from liver which attacks the product of enzymatic oxidation of 3-hydroxyanthranilic acid. Earlier studies have indicated a sequence of reactions proceeding form tryptophan through formylkynurenine, kynurenine, 3-hydroxykynurenine and 3-hydroxyanthranilic acid to be involved in the biosynthesis of niacin. The two reactions being studied are the only known enzymatic reactions that continue this series, and therefore they must be studied to furnis an understanding of the mechanism of niacin synthesis.

Significance to NIAMD Research; The conversion of tryptophan to nicotinic acid is quantitatively important in man and laboratory animals. The present study is part of an attempt to elucidate the mechanisms involved in this transformation. Such information aboutthis and other systems is necessary for an understanding of nutritional requirements and influences of diet and disease on nutritional requirements. At another level, it has already been shown that

Project Description Sheet Continued

cortisone has a rapid dramatic effect on the level of the enzyme which oxidizes tryptophan. The relation between this effect of cortisone and its other biological effects is not yet clear, but there is hope that more information at the enzyme level will help determine the mechanism of cortisone action.

Proposed Course of Project: Purification of the two enzymes concerned with 3-hydroxyanthranilic acid oxidation will be continued, and studies will be directed towards elucidation of the structures of the intermediate and final products. Attempts will be made to obtain cell-free systems to carry out the oxidation of kynurenine to 3-hydroxykynurenine, and earlier step in the biosynthesis of nicotinic acid.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62125-77
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	6,900	2/3		2/3	2/3		2/3	
FY 1956	8,000	1		1	1		1	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62125-77
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Tryptophan Metabolism. Chapter in Symposium on Amino Acids, edited by W. D. McElroy and B. Glass. The Johns Hopkins Press, Baltimore (In press).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Laboratory of Physical Biology
LABORATORY OR BRANCH

3. Molecular Biophysics
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NIAMD- 62126-78
SERIAL NO.

6. The physical chemistry of membranes and complex membrane systems of biological interest.
PROJECT TITLE

7. Dr. Karl Sollner
PRINCIPAL INVESTIGATOR(S)

8. Dr. Rex Neihof and Dr. Sheldon Dray. Dr. Gottlich and Dr. Wagner
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: A physicochemical study of membranes and membrane model systems, with the purpose of providing a rational physicochemical basis for the elucidation of numerous phenomena in living organisms, for instance, electrolyte balance and electrolyte distribution, the accumulation of electrolytes in living cells, cell and nerve potentials, and electrophysiology in general.

Methods Employed: The preparation of membranes of highly characteristic and specific electrochemical properties (the methods having been worked out by the principal investigator and his collaborators), and the investigation of these membranes by physicochemical, especially electrochemical methods, such as potential and resistance measurements, also by chemical analytical procedures, including radioactive tracer methods.

Major Findings: A mechanism was suggested which explains the accumulation of electrolyte, both cations and anions, against concentration gradients. It involves two Donnan membrane equilibria that arise independently across a cation-permeable, anion-impermeable permselective membrane and an anion-permeable, cation-impermeable permselective membrane which separate an "inside" and an "outside" solution, the system being electrically a 3-compartment arrangement, but a 2-compartment arrangement with respect to concentration. Experimental tests have shown a 20-fold accumulation of electrolyte. (Sollner.)

9. PROJECT DESCRIPTION - CONTINUED

It was shown that the dynamic membrane potentials which arise in systems with three and more coexisting species of ions of the same sign of charge and with appropriate permselective membranes can be precalculated with a high degree of accuracy on the basis of previously developed concepts. (Dray and Sollner.)

A theory was tentatively worked out which explains on a strictly physicochemical basis the differential accumulation of different species of ions of the same sign of charge across a permselective membrane, for instance, the preferential accumulation of potassium over sodium, or of iodide over chloride.

Significance: In order to understand electrolyte relationships in living cells and tissues, it is necessary to have accurate information on membrane model systems which, under carefully controlled known conditions, reproduce at least some of the major *in vivo* phenomena. The *in vitro* model of electrolyte accumulation constructed during the current year is the first instance in which a nonliving system accumulates both anions and cations simultaneously against concentration gradients, thus simulating one of the most basic and most common cell activities.

The study of polyionic potentials in synthetic membrane systems was put on a general rational basis which might be an opening wedge in the clarification of many basic questions in electrophysiology such as resting and action potentials.

Proposed course of project: Completion of the work on bi- and polyionic potentials (Dray and Sollner). Continuation of the work on the preparation of strong base type membranes (Gottlieb, Neihof and Sollner). Continuation of the studies on the kinetics of the rate of exchange of ions across membranes of high ionic selectivity and the correlation of these rates to other properties (resistance) of the membranes (Gottlieb and Sollner). A study of concentration cells involving the bivalent alkaline earth cations and the recently developed strong acid type sulfonated polystyrene collodion membranes (Wagner & Sollner). Continuation of the experimental test of the above-indicated theory of differential absorption of ions of the same sign of charge.

December 1954 Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD- 62126-78
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	26,900	3		3	3		3	
FY 1956	26,900	3		3	3		3	

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12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 10)

Dr. Melvin Gottlieb, Laboratory of Kidney and Electrolyte Metabolism, National Heart Institute, is assigned to the laboratory of the principal investigator and carries out under the latter's supervision the study on the kinetics of membrane systems. He also participates in the preparation of strong base type membranes.

Dr. Josef Wagner of Vienna, Austria, assigned through the Institute of International Education to the principal investigator's laboratory. (See above.)

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD- 62176-78
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Gregor, H. P. and Sollner, K., The potentiometric determination of cations and anions with permselective collodion and protamine-collodion membrane electrodes. J. Phys. Chem. 58, 409-415 (1954).

Sollner, K., with Sheldon Dray, Eugene Grim, and Rex Neihof, Electrochemical studies with model membranes, in "Ion Transport Across Membranes," edited by Hans T. Clarke, Academic Press, New York, 1954. pp. 144-188.

Neihof, Rex, The preparation and properties of strong acid type collodion-base membranes. J. Phys. Chem. 58, 916-925 (1954).

Sollner, K., The electrochemistry of porous membranes, in "Electrochemistry in Biology and Medicine," edited by Theodore Shedlovsky, John Wiley & Sons, New York. In Press.

Sollner, K., Sheldon Dray, Eugene Grim, and Rex Neihof, Membranes of high electrochemical activity in studies of biological interest, in "Electrochemistry in Biology and Medicine," edited by Theodore Shedlovsky, John Wiley & Sons, New York. In press.

Sollner, K., A physicochemical cell model which simultaneously accumulates anions and cations against concentration gradients, Arch. Biochem. and Biophys. In press.

Sollner, K., Discussion of the paper, "Biophysical Effects of Ultrasonic Energy on Carcinoma and their Possible Significance," by Justus F. Lehmann, Julia F. Herrick, and Frank H. Krusen, delivered before the Thirty-second Annual Scientific and Clinical Session of the American Congress of Physical Medicine and Rehabilitation September 10, 1954, Washington, D.C. In press.

Neihof, R. and Sollner, K., A quantitative electrochemical theory of the electrolyte permeability of mosaic membranes composed of selectively anion-permeable and selectively cation-permeable parts, and its experimental verification. II. A quantitative test of the theory in model systems which do not involve the use of auxiliary electrodes. J. Gen. Physiol. In press.

NIAMD- 62126-78
SERIAL NO.

16. PUBLICATIONS - CONTINUED

For limited circulation only:

Dray, Sheldon, A quantitative theory of dynamic polyionic potentials across membranes of ideal ionic selectivity in terms of transference numbers and its experimental test with permselective membranes, Ph.D. Thesis, University of Minnesota, 1954. 223 typewritten pages.

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Laboratory of Physical Biology
LABORATORY OR BRANCH

3. Molecular Biophysics
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NIAMD- 62126-79
SERIAL NO.

6. Investigation of the macromolecular organization of living matter.
PROJECT TITLE

7. Dr. R. W. G. Wyckoff
PRINCIPAL INVESTIGATOR(S)

8. Dr. Louis W. Labaw, and Mr. V. M. Mosley
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To gain information about the macromolecules that are essential constituents of living matter - to see how they are arranged in the structures they form and to see how this arrangement is altered by infectious and degenerative disease. To study certain of these macromolecules (such as viruses) in purified form after isolation from the living material.

Methods Employed: The electron microscopy of microorganisms, cells, and tissues in suspension or thinly sectioned; the physicochemical characterization of macromolecular components isolated from such material using electron microscopy, X-ray diffraction and similar established techniques; the development of new physical procedures to further such characterization.

Major Findings: The work carried out in Bethesda during the last year has been devoted mainly to the discovery and investigation of unexpectedly well-ordered macromolecular structures in certain bacteria. Thus, in connection with our studies of the bacteriophages of the colon bacillus, a strain of the latter has been found with a capsule made up of striated fibers, rather than the usual amorphous gel. We have also found, and are studying in greater detail, bacteria with cell walls made up in part of perfectly ordered spherical macromolecules and with flagella that

9. PROJECT DESCRIPTION - CONTINUED

are helical structures showing an underlying regularity in macromolecular composition.

During the last two years one of the principal investigators (Ralph W. G. Wyckoff) has been serving as Science Attache at the U. S. Embassy in London. While there he has worked, partly as consultant to the NIH, and in collaboration with confreres at University College, London, and the Pasteur Institute, Paris, to develop methods for examining at electron microscopic magnifications tissues of the central nervous system before and after infection with neurotropic viruses. These investigations, which are to be continued here, have thus far shown new facts important to an understanding of the structure of healthy nerve tissue and of the growth of rabies and poliomyelitis in this tissue.

Significance to NIAMD Research: Planned as a program of fundamental research, most of our results will only later be applicable to the specific pathological conditions, such as arthritis, with which this Institute is concerned. The studies we have made of the macromolecular texture of collagen is, however, already providing fundamental background for interpreting pathological changes in connective tissue.

Proposed course of project: Besides the foregoing, emphasis for the immediate future is to be laid on (1) the further development of methods of electron microscopy to reveal increasingly small detail in biological structures, (2) the development of X-ray microscopy as a way of getting new information about the interrelations of structures of macromolecular importance, and (3) the exploration of certain new physical microprocedures which may give new chemical information about these structures.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD- 62126-79
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	43,400	3	3	6	3	3	6	
FY 1956	43,400	3	3	6	3	3	6	

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12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 10)

None

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD- 62126-79
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Labaw, L. W. and Mosley, V. M.: Demonstration of striated fibers in the capsule of the Lisbonne strain of lysogenic Escherichia coli. J. Bact., 67: 576-584, May 1954.

Labaw, L. W. and Mosley, V. M.: Periodic structure in the flagella and cell walls of a bacterium. Biochim. et Biophys. Acta, 15: 325-331, Nov. 1954.

Noda, Haruhiko: The dimensions of T series bacteriophages of Escherichia coli B. Biochim. et Biophys. Acta, 12: 495-498, Dec. 1953.

Wyckoff, Ralph W. G.: Electron microscopic evidence on virus proliferation. (Symposium on the interaction of viruses and cells.) 6th International Congress of Microbiology, Rome, Italy. September 7-11, 1953.

Wyckoff, Ralph W. G.: The Electron Microscope in Biology. The Year Book of The Royal Institution of Great Britain. Nature, 173: 419, 1954.

Wyckoff, Ralph W. G.: Some thoughts on the future of natural science, with illustrations from the growth of X-ray diffraction work in the United States. Brit. J. Appl. Physics, 5: 199-204, 1954.

Wyckoff, Ralph W. G.: Introduction to Symposium on Sub-Microscopic Organization of Cytoplasm. (Leiden, The Netherlands - September 1-8, 1954.) To appear in Proc. of the VIIIth Congress of Cell Biology.

Young, J. Z. and Wyckoff, Ralph W. G.: The Motorneuron Surface. (In press)

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Ralph W. G. Wyckoff - President, International Union of Crystallography
Ralph W. G. Wyckoff - President, Joint Commission (of ICSU) on Electron Microscopy.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Laboratory of Physical Biology
LABORATORY OR BRANCH

3. Photobiology
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NIAMD- 62127-80
SERIAL NO.

6. Ionization studies in the upper atmosphere.
PROJECT TITLE

7. Dr. Herman Yagoda
PRINCIPAL INVESTIGATOR(S)

8. Howard B. Smith, Jr.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The study of the characteristics of fundamental particles created in the interaction of high energy ($\gtrapprox$ 2 Bev) cosmic ray particles with air nuclei. This is primarily of importance in our understanding of nuclear forces and meson physics. The subject is also of biological significance in the interpretation of the radiation hazards associated with high altitude (60,000 ft. and up) manned vehicles.

Methods Employed: Exposure of nuclear emulsions in rockets and high altitude balloons (Skyhooks).

Major Findings: Of current theoretical interest is the formation of nuclei with one of the neutrons substituted by a lambda-particle. We have made an important finding in showing the mesonic decay of an excited triton from which it was possible to deduce the binding energy of the lambda-particle in this strange nucleus.

Our observation of the crossing of a relativistic carbon nucleus through tissue has proven of interest to the U. S. Air Force (see report by Major David G. Simons, U.S.A.F.(MC) published in the J. Aviation Med. 25, 380 (1954)).

9. PROJECT DESCRIPTION (Continued)

Significance to NIAMD Research: Basic research which may have significance of military or health importance.

Proposed Course of Project: In an effort to establish the number of heavy primary hits passing through maximum ionization in tissue, a phantom of a human head is to be flown by the U. S. Air Force in the spring of 1955. This will contain emulsion detectors for establishing the number of "thin-down hits" (believed to be the greatest radiation hazard from cosmic radiation) in the brain and the eyes.

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD- 62127-80
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	14,700	1	1	2	1	1	2	
FY 1956	14,700	1	1	2	1	1	2	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 10)

Cooperating Units: 1. Naval Research Laboratory Rocket Sonde.
2. Office of Naval Research Balloon Project.
3. U. S. Air Force.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD- 62127-80
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

H. Yagoda, Occurrence of a fission-dust particle in a nuclear emulsion, Nature 173, 79 (1954). Also New York Times, Jan. 9, 1954, page 1.

H. Yagoda and Howard B. Smith, Jr., Observations on the penetration of a heavy primary through tissue, J. Aviation Med. 25, 46-49 (1954).

H. Yagoda, Memorial of Olan I. Lee, Amer. Mineralogist 39, 277-279 (1954).

H. Yagoda, Isothermal processing of thick nuclear emulsions, Rev. Scientific Inst. In press.

H. Yagoda, Tracks of nuclear particles, Scientific American. In press.

H. Yagoda, Pion-pair production in a nuclear emulsion, Physical Rev. In press.

H. Yagoda, Mesonic-decay of an ejected triton, Physical Rev. In press.

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Laboratory of Physical Biology
LABORATORY OR BRANCH

3. Photobiology
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NIAMD- 62127-81
SERIAL NO.

6. Investigations of the action of radiant energy on biologically important compounds, with emphasis on steroids.
PROJECT TITLE

7. Dr. Norman E. Sharpless and Dr. F. S. Brackett
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objectives of this project are the establishment of the structures of the various products and intermediates of the steroids and the kinetics and quantum efficiencies of their alteration by radiant energy.

Also during the past year a series of studies was completed on the high energy radiation of aqueous solutions of amino acids.

Methods employed: Methods utilized consist of the ultraviolet irradiation, analysis, and isolation of the products, using physico-chemical and physical techniques including ultraviolet and infrared spectroscopy, X-ray diffraction and optical rotations.

Major Findings: The preparation and isolation of vitamin D intermediates on a macro scale by the irradiation of ergosterol is a function of the physical set-up of the radiation and circulation equipment. The ratio between thickness of absorbing layer and the speed of circulation must be nicely balanced to give maximum yields of the desired products.

Commercial ergosterol has a tendency to turn yellowish on storage, especially in the air and light. Preliminary investigation of the

9. PROJECT DESCRIPTION - CONTINUED

nature of the products formed seems to indicate that it consists of a carbonyl compound of some type.

In the just completed study on the effects of high energy radiation on aqueous amino acids, there was found a general tendency for such radiation to react with the various acids to give analogous products. In general there is deamination to give the corresponding fatty acids and keto acids, deamination plus decarboxylation to give the aldehyde and decarboxylation to give the amine. In the cases of glycine and alanine these reactions occur with the same frequencies.

Significance to NIAMD Research: A knowledge of the fundamental properties of the various biologically active materials is absolutely necessary for the complete understanding of their action in the cell, and is required for the discovery of supplemental or similar acting substances.

Proposed Course of Project: An intensive investigation of the infrared spectra of compounds related to those showing vitamin D activity, in an attempt to correlate structural and chemical factors with biological activity.

An instrument is being developed which will record the infrared spectrum in the region of 3 μ at high resolution. This is expected to yield information on hydrogen bonding of significance in this study.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD- 62127-81
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	20,300	2½	1½	4	1½	1½	3	
FY 1956	23,300	2½	1½	4	2½	1½	3	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 10)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD- 62127-81
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Svirbely, W. J. and N. E. Sharpless, The quenching of the fluorescence of the eosin ion, J. Am. Chem. Soc. 76, 1404 (1954). (From the Ph.D. Thesis of N. E. Sharpless--published through the University of Maryland.)

Maxwell, C. R., D. C. Peterson and N. E. Sharpless, The effect of ionizing radiation on amino acids. I. The effect of X-rays on aqueous solutions of glycine, Rad. Research 1, 530 (1954).

Sharpless, N. E., A. E. Blair and C. R. Maxwell, The effect of ionizing radiation on amino acids. II. The effect of X-rays on aqueous solutions of alanine. Accepted for publication in Rad. Research.

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Laboratory of Physical Biology
LABORATORY OR BRANCH

3. Photobiology
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NIAMD- 62127-82
SERIAL NO.

6. Effects of radiant energy on the oxidative metabolism and chemosynthesis in living cells
PROJECT TITLE

7. Dr. R. A. Olson and Dr. F. S. Brackett
PRINCIPAL INVESTIGATOR(S)

8. R. Crickard
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To study the specific effects of radiant energy on cellular oxidative metabolism and chemosynthesis utilizing the ultraviolet, visible, and infrared regions of the spectrum. To determine the role and identity of enzymes, photosensitizers, and pigments in the photochemical and other reactions involved. In addition, to identify the intracellular morphological changes associated with such metabolic effects in order to localize reaction sites and participating cell structures or inclusions.

Methods Employed: Cell suspensions of unicellular organisms (Chlorella, etc.) cultured aseptically under various experimental conditions are irradiated in monochromator systems designed to permit homogeneous radiation of all cells. Special features are also provided to overcome the prevailing difficulties in the measurement of the energy absorbed by cells introduced through the nonselective scattering of light by such suspensions. Similarly the selective absorption and identity of pigments and other components is determined accurately in living cells. Simultaneous electrochemical

NIAMD- 62127-82
SERIAL NO.

9. PROJECT DESCRIPTION - CONTINUED

measurements of oxygen metabolism during prescribed radiation and dark intervals under various conditions of intensity, wavelength, added substrate, specific enzyme inhibitors, and pigment density provide quantum and kinetic data leading to the identity and nature of the photochemical and dark reactions involved. High resolution monochromatic photomicrography provides morphological data.

Major Findings: Methods developed for culturing cells under conditions which may control pigment density without limiting other aspects of normal growth and metabolism have established the dependence of quantum efficiency upon both pigment density and the relative proportion of pigment components.

Morphological effects such as cell size, pigment distribution and localization of storage products in the cell have been likewise associated with conditions governing pigment density and quantum efficiency.

Additional developments include: (1) a method for rapid automatic recording simultaneously of the rate of oxygen exchange of cell suspensions and the oxygen concentration; (2) an integrating sphere differential recording spectrophotometer for use with living cell suspensions; (3) the adaptation of high intensity radiation sources for D.C. operation to provide steady and unmodulated monochromatic radiation at desired wavelengths; and (4) the utilization of the high speed micro-ball mill technique to obtain efficient disruption of mechanically resistant cells for complete extraction or separation of cell components.

Significance to NIAMD Research: Unicellular organisms with special metabolic adaptation for the utilization of radiant energy in chemosynthesis carry out to a marked degree but by different pathways the same general metabolic reactions which occur in the more specialized cells of higher organisms. During the synthesis of proteins, fats, oils, steroids and other cell components some mechanism for CO_2 assimilation is now considered to be operable in the normal metabolism of all cells. In cells not adapted to utilize radiant energy the energy source for this process is provided chemically via phosphate or other energy transferring systems. Radiant energy thereby becomes a tool in photosynthetic organisms by which specific metabolic pathways may be induced at will without changing in any other way the physical or chemical environment of the cell. Use of the appropriate wavelength and intensity of radiation may provide considerable choice in the degree of participation by known pigments in both synthesis and

9. PROJECT DESCRIPTION - CONTINUED

oxidative reactions while the duration and intensity of light allows for a kinetic study of the carboxylation-decarboxylation equilibrium. Information in this direction leads to a better understanding of the more subtle metabolic pathways which characterize anomalies in physiologically diseased cells.

Proposed Course of Project: Completion of the work involving quantum efficiency dependence upon quantitative and qualitative pigment development. Further emphasis on specific inhibitor and substrate effects and wavelength dependency of oxidative metabolism via pigment participation. Improvement of present electrochemical oxygen detection method and extension to include CO_2 measurement in cell suspensions.

Continuation of time course and kinetic studies of photo-induction lag under various conditions conducive to identity of the responsible process. Continuation of morphological studies with enhancement by appropriate histochemical techniques.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD- 62127-82
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	36,600	2½	3½	6	2½	3½	6	
FY 1956	36,600	2½	3½	6	2½	3½	6	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 10)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD- 62127-82
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Olson, R. A. Physiological action of auxin, Physiol. Reviews (Accepted for publication).

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities
Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Laboratory of Physical Biology
LABORATORY OR BRANCH

3. Radiation Safety
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NIAMD- 62128-83
SERIAL NO.

6. Radiation safety; metabolism of radioactive materials
PROJECT TITLE

7. Victor E. Archer
PRINCIPAL INVESTIGATOR(S)

8. Walter C. Cool
Joseph M. Brown
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To provide service and supervision which will promote the safe use of radiation at the NIH; to develop improved methods of radioactive decontamination and waste disposal; to determine the uptake, retention and excretion of certain radioactive materials and how this is affected by various factors such as isotope dilution and infections.

Methods Employed: Surveys of radiation producing machines and laboratories where radioactive materials are used; receiving, checking, calibrating and delivering isotope shipments; collecting radioactive waste; doing physical exams and blood counts; tracer studies on decontamination and waste disposal; the metabolism studies are done primarily with experimental animals, but may be done on individuals who have had an accidental intake of radioactive materials.

Major Findings: The exponential decrease with time of the excretion of radium by humans was further delineated; tuberculous animals were found to metabolize radioiodine differently than normals; large doses to animals of a stable isotope of an element was found in some cases to affect the metabolism of its radioactive isotope even though the element was not a trace element; the demonstration that radioiodine enters infarcted myocardium nearly as rapidly as it enters normal myocardium.

9. PROJECT DESCRIPTION - CONTINUED

Significance to NIAMD Research: All knowledge of the metabolism of radioactive substances is applicable to a greater or lesser extent to normal metabolism which must be understood to study metabolic diseases; a possible development is a new method of therapy for accidental intake of radioactive substances.

Proposed course of the project: Continue the radiation safety service as in the past; continue the search as to the cause of the difference in metabolism of radioiodine in tuberculous and normal animals; expand the study of "isotopic flooding" to other elements; continue the work on decontamination of electrolysis.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD- 62123-83
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	24,300	1	3	4	1	3	4	
FY 1956	24,300	1	3	4	1	3	4	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 10)

Section on Mycotic and Bacterial Diseases, NMI, under Dr. Byron J. Olson will contribute personnel and facilities with regard to the studies on infected animals. Serial number 72116.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

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December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD- 62123-83
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Looney, W. B. and V. E. Archer. Radiation inhalation accident--radium excretion study. Accepted by Am. J. Roentg. Rad. Therap.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Laboratory of Physical Biology
LABORATORY OR BRANCH

3. Physiology
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NIAMD- 62129-84
SERIAL NO.

6. Pulmonary ventilation
PROJECT TITLE

7. Heinz Specht
PRINCIPAL INVESTIGATOR(S)

8. Howard F. Brubach
Loyal G. Goff
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The studies in pulmonary ventilation at this Laboratory have resulted from observations made in low and normal density atmospheres. Studies in high density atmospheres are now in progress as embodied in a subproject on the physiology of underwater swimmers.

Objectives: The principal objective of the over-all project is to explore new phenomena regarding breathing behavior with regard to their physiological significance. In order to accomplish this various studies of physiology must be undertaken in order to accurately control the experimental situation. Thus, in underwater swimmers it is hoped that ultimately breath velocity patterns at various depths may yield information that can be compared with our studies at high altitude. As interim objectives the physiology of finned underwater swimmers is being studied on contract to the Office of Naval Research. This is the third year of such support.

Methods Employed: Subjects are studied for oxygen consumption, CO_2 production, breath velocity patterns, and other responses as necessary while swimming or resting immersed under accurately known conditions of temperature, water speed, drag, etc. Since conditions under water are less amenable to volumetric gas measurement than in

9. PROJECT DESCRIPTION - CONTINUED

the classical metabolic studies in air it has been necessary to devise special equipment for the various measurements. In addition, swimming facilities had to be set up for use in the laboratory as an alternate to the use of the circulating water channel of the David Taylor Model Basin which was placed at our disposal for limited periods in the past.

Major Findings: The average efficiency of underwater swimming in this series did not exceed 5.1%. This was calculated on the basis of the difference between oxygen consumption during the drag measurements when swimmer activity was at a minimum and the oxygen consumption at known swim rates, compared with the actual work accomplished as determined by the drag data. At the highest swim rate (1.0 knot) the average work accomplished was about 800 ft. lb./min. This corresponds to light work in air. The measurements of oxygen consumption, respiratory minute volume and breath velocity, however, fall well within the known ranges for heavy work in air.

For long distance swimming a rate of 0.7 knots seems to be optimum under the conditions of this series of tests. At this rate swimming efficiency was maximum (5.1%) as was the coefficient of oxygen utilization (48 cc/liter of ventilation) and the calculated oxygen consumption per mile was lowest (approximately 70 l.).

Significance to NIAMD Research: In order to extend the understanding of both normal and abnormal respiratory gas exchange it has become necessary to explore the significance of phenomena beyond those used classically for measuring pulmonary function. Inasmuch as physical environment affects such phenomena the study of atmospheric density effects on breathing will ultimately form a new set of criteria for judging the level of normal or abnormal behavior.

Proposed course of project: The contract with ONR on underwater swimmers is for 2 years. It is hoped that by that time the basic information on breathing patterns will be in hand. It is planned that studies with artifically mixed atmospheres of various density to simulate the effect of depth can be set up for further research. A beginning has been made with sulfur hexafluoride, but certain technical and toxicological difficulties must first be overcome.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD- 62129-84
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	34,100	2	4	6	2	3	5	
FY 1956	34,100	2	4	6	2	3	5	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANI-ZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 10

This project is being carried partly by funds from the Office of Naval Research during 1955 and 1956.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD- 62129-84
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

There are no publications from this project. Reports have been sent directly to ONR on progress of the contract.

Black, Simon. Enzymatic reduction of β-aspartyl phosphate to homoserine. J. Am. Chem. Soc., 75: 5766, 1953. (Not reported in 1953 Annual Report.)

Smith, W. W., L. Gonshery, I. Alderman and J. Cornfield. Effect of granulocyte count and litter on survival of irradiated mice. Am. J. Physiol., 178: (3) 474-476, Sept., 1954.

Smith, W. W., R. Q. Marston and J. Cornfield. Granulocyte count, resistance to experimental infection and spleen homogenate treatment in irradiated mice. Am. J. Physiol., 178: (2) 288-292, Aug., 1954.

Smith, W. W., W. Anderson and G. Ashwell. Spleen adenosine triphosphatase activity in irradiated mice treated with spleen homogenate. Am. J. Physiol., 178: (3) 471-473, Sept., 1954.

Smith, F., W. W. Smith, L. Gonshery and M. M. Grenan. Effect of immunity on resistance to infection in irradiated mice and rats. Proc. Soc. Exptl. Biol. Med., 87: (1) 23-26, Oct., 1954.

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Laboratory of Physical Biology
LABORATORY OR BRANCH

3. Physiology
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NIAMD- 62129-85
SERIAL NO.

6. Physics of gas diffusion into and through tissues
PROJECT TITLE

7. John B. Buck
PRINCIPAL INVESTIGATOR(S)

8. Margaret L. Keister
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: Our objective is to learn as much as possible about the physical factors which govern the passage of respiratory gases through biological structures, particularly in the gas phase and in the region of phase change, where gases enter and leave tissues. This involves the study of tissue permeability, mechanism of diffusion, and respiratory responses to various gas concentration gradients.

Methods Employed: We have used insect material because it is amenable to much more drastic experimental alteration than that of any other air-breathing animal, and yet resembles lung-breathing vertebrates in having a direct tissue-gas exchange. Furthermore, in many instances respiration has been simplified to pure diffusive transfer, which is thus susceptible to precise analysis.

Major Findings: Analysis of two problems was completed during the past year. The first involved the mechanism of gas passage through the minute respiratory valves, the problem being raised by the fact that ordinary diffusion was calculated to account for only 10% of the observed oxygen uptake. Analysis showed that an unusual process, "pore-diffusion", hitherto known only in the green leaf, is responsible for the paradoxically high rates of gas passage. The second problem concerned certain insects which, at basal metabolic levels, impound from 60 to 100% of their respiratory CO_2 for long periods, during which O_2 uptake is steady and normal, then release the impounded CO_2 in

9. PROJECT DESCRIPTION - CONTINUED

in great gushes. The CO_2 retention was found to involve both mechanical damming by the air valves and CO_2 stabilization by tissue buffers, and to be primarily the result of provisions for water conservation.

Significance to NIAID Research: Aside from their contribution to understanding of the little-known field of gas-liquid phase exchange in respiration, our studies have impinged directly on three aspects of human respiratory physiology. (a) the "pore-diffusion" analysis was useful in evaluating and suggesting methods of investigating the possibility (recently suggested by McClendon) that pore diffusion occurs through the alveolar necks of the lung; (b) the "CO_2 gush" analysis shed light on the analogous gas exchange taking place in the human lung during breath-holding. (c) Some cooperative work we undertook with Dr. Jacob Verduin of Ohio State University stimulated him to make some new estimates of pulmonary gas transfer which cast doubt on accepted estimates of gas passage across the alveolar membrane.

Proposed course of project: Future projects planned include (a) tissue pO_2 distribution in hypoxia, and (b) physical mechanisms of water retention.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD- 62129-85
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	17,000	1	1	2	1	1	2	
FY 1956	17,000	1	1	2	1	1	2	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 10)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD- 62129-85
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Buck, J. B. Bioluminescence. In press in a symposial volume of the A.A.A.S.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954.

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Laboratory of Physical Biology
LABORATORY OR BRANCH

3. Physiology
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NIAMD- 62129-86
SERIAL NO.

6. The effect of synthetic plasma expanders on renal hemodynamics in dogs
PROJECT TITLE

7. Louise H. Marshall
PRINCIPAL INVESTIGATOR(S)

8. Charles H. Hanna
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: Two principal objectives are served by a study of the effect of simultaneous administration of the synthetic plasma expanders, dextran and polyvinyl pyrrolidone (PVP). The first is to determine the capacity of the healthy dog's kidney to continue normal function under stress. This condition occurs during glomerular filtration of large amounts of the smaller molecular sizes of the injected colloid. Excretion of a second colloid at this time may alter renal function.

The second objective concerns the possibility that with 2 synthetic plasma expanders available in time of emergency they might be used in the same person. Nothing is known of their compatibility.

Methods Employed: Renal clearances are determined of test substances which are accepted as measures in the dog of glomerular filtration, effective renal plasma flow, and tubular capacity for secretion and reabsorption. After a colony of dogs having normal values is established, they will be subjected to massive rapid injections of PVP, followed by dextran. When excretion of these colloids is at a maximum, renal function will be retested. Blood pressure will be followed to make sure that it remains within normal limits. Blood and urine concentrations of the expanders in addition to the clearance substances will be determined. Extraction should also be measured, which necessitates renal vein catheterization. If facilities permit, the question of colloid storage should be studied by means of tissue analysis and histological sectioning.

9. PROJECT DESCRIPTION - CONTINUED

Major Findings: Several details of experimental procedures have been clarified this year, and are the subjects of 3 publications now in preparation. In order to inject massive doses of PVP into dogs without producing an extreme fall in blood pressure which would suppress urine formation, it was necessary to find out whether they could be desensitized. A series of graded doses, with duplication of the final massive dose was successful.

The causes of a disproportionately large decrease in hematocrit value of the second blood samples in a series were found. This was important because the hematocrit value enters into the calculation of renal blood flows measured by clearance methods.

The lack of published corrections for dogs' blood of sedimentation rates at various hematocrit values made it necessary to collect our own. This will make it possible to determine whether an increase in erythrocyte sedimentation rate is due to dilution or to the plasma expander per se.

Significance to NIAMD Research: The significance of this project for the Institute lies in the clarification which may be gained of normal renal hemodynamics, which is the basis for an understanding of pathological conditions. The fact that dogs are sensitive to PVP and not to dextran makes a combination of these substances an interesting problem in cellular permeability.

Proposed course of project: We do not expect to undertake our major project until the laboratory has moved. Until then, we will be occupied with obtaining normal clearances to be used as baseline values, at the same time accustoming the dogs to the procedure. Renal vein catheterization technique is still to be practiced, and arrangements made for histological studies by ourselves or others.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD- 62129-86
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	17,500	1	2	3	1	2	3	
FY 1956	17,500	1	2	3	1	2	3	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 10)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honor , Awards, and Publications Sheet

15. NIAMD- 62129-86
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Marshall, L. H. and C. H. Hanna. Differences in T-1824 and erythrocyte concentration of venous blood of dogs after dextran. Am. J. Physiol., 176: (2) 331-334, Feb., 1954.

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1962 Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Laboratory of Physical Biology
LABORATORY OR BRANCH

3. Physiology
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

6. NIAMD- 62129-87
SERIAL NO.

6. Effects of hypoxia on physiologic mechanisms
PROJECT TITLE

7. Paul D. Altland
PRINCIPAL INVESTIGATOR(S)

8. Edwin C. Thompson
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: Subproject a. Increased erythropoiesis occurs in animals bled repeatedly, following cobalt administration or as result of exposure to hypoxia but the mechanism of action is unknown. Studies are being conducted using varying degrees of these three procedures in order to obtain a better understanding of factors stimulating blood formation. The presence of an humoral (hematopoietin) has been postulated as being the primary substance stimulation erythroid bone marrow. A search for this substance in dogs is being conducted. The longevity of the erythrocyte of various animals is being investigated in order to shed some possible light on the factors responsible for the formation of new erythrocytes.

Subproject b. Repeated exposure of rats to simulated altitude increase their susceptibility to experimental bacterial endocarditis. A method, similar to the one developed by Highman and Altland for rats, is being developed with larger animals in order to learn more of this common form of heart disease which, despite intensive antibiotic therapy, has a current mortality of 10 to 30%. The influence of hypoxia on the susceptibility of mice to malaria is being studied.

Subproject c. Because of the ever expanding functions of civilian and military aviation, studies on the fundamental mechanisms of natural adaptation to high altitude and of means of increasing hypoxic tolerance by artificial means such as pharmacologic and dietetic are being conducted. Specifically, acclimatization responses of dogs and hamsters and the effects of a high fat diet on altitude acclimatization are being determined.

9. PROJECT DESCRIPTION - CONTINUED

Methods Employed: The varying degrees of hypoxia are produced by exposing animals to reduced atmospheric pressures in 2 altitude chambers. Histochemical, hematological, and radiobiological methods are used in the various studies.

Major Findings: Hypoxia, which has been previously thought to act as the fundamental stimulus for erythropoiesis in all vertebrates, has been found to be ineffective as a stimulus to blood formation in cold-blooded animals such as the turtle. Furthermore circulatory and respiratory adjustments to acute exposure to hypoxia, which are characteristic of all homiotherms, are not found in the turtle. A possible explanation for the marked resistance of the turtle erythrocyte to damage by whole-body X-irradiation may be in the finding that the longevity of the turtle erythrocyte is many times longer than any other animal previously reported in the literature.

There is no increased susceptibility of rats to experimental bacterial endocarditis if polycythemia is prevented by repeated bleedings during the period of exposures to altitude. The resistance of rats is not lowered by a diet containing cobalt, which produces polycythemia but not hypoxia. These findings suggest that polycythemia acts by increasing the work load of the heart and that hypoxia lowers the resistance to certain bacteria, and that both such factors are needed to render a normal heart more susceptible to infection.

Significance to NIAMD Research: Provides information for a better understanding of the relationship of metabolism and blood formation. Supplying a method for evaluation of various factors important in the development and treatment of cardiovascular diseases.

Proposed course of project: Attempts will be made to find a cold-blooded animal representative of a class other than reptiles to be used to provide further data on the relation of hypoxia to blood formation and physiologic adaptations. Preliminary evidence now suggests that it is possible that erythrocyte longevity may be correlated with species longevity in poikilotherms. Studies will be conducted in order to substantiate this hypothesis.

Further attempts will be made to render dogs susceptible to experimental bacterial endocarditis for the purpose of providing a tool for the surgical, physiological and therapeutic studies. Further attempts to influence the course of experimental malaria will be conducted with various strains of mice found to show marked variation in their erythropoietic response to hypoxia.

Work will continue on the in vivo production of erythropoietin in dogs.

The studies on the altitude acclimatization of obese rats will be continued, and the subject of factors affecting altitude tolerance is being thoroughly explored.

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD- 62129-87
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	23,300	1	3	4	1	3	4	
FY 1956	23,300	1	3	4	1	3	4	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 10)

Studies on longevity of erythrocyte are being conducted with cooperation of Dr. Kirkland Brace of General Radiobiology Section, National Cancer Institute.
NIAMD -
Studies on hematopoietin in dogs conducted in cooperation with Drs. Charles M. Sinn, Paul Rogan, and C. Lockard Conley of the Department of Medicine of The Johns Hopkins Hospital, Baltimore, Maryland.

Endocarditis studies conducted with cooperation of Dr. Benjamin Highman of Section on Pathologic Anatomy, NIAMD.- 62112-62

Studies with obese animals are being conducted with cooperation of Dr. Olaf Mickelsen of Section on Biochemistry and Physiology of Nutrition, NIAMD.
NIAMD-62113-12

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD- 62129-37
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Altland, P. D. and B. Highman. Effect of a folic acid antagonist (9-Methyl PGA) upon rats exposed to high altitude. Am. J. Physiol., 176: (1) 1-5, Jan., 1954.

Altland, P. D. and M. Parker. Effects of hypoxia upon the box turtle. Accepted by Am. J. Physiol.

Highman, B., P. D. Altland and H. Eagle. Experimental bacterial endocarditis in altitude rats. AMA Arch. Path., 58: 241-257, Sept., 1954.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Laboratory of Physical Biology
LABORATORY OR BRANCH

3. Physiology
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NIAMD- 62129-88
SERIAL NO.

6. To investigate the metabolic responses to stress and to drugs of intact cells and tissues
PROJECT TITLE

7. Frederick Sperling
PRINCIPAL INVESTIGATOR(S).

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: Tagging the cellular components (fats, proteins, amino acids, nucleic acids, etc.) with C^{14} and analysing the changes in the C^{14} and analysing the changes in the C^{14} content of these components after exposure to drugs and to stress.

Methods Employed: The primary components (fats, proteins, etc.) of frog eggs were made radioactive by injecting the female with formate-C^{14}. Ovulation was then induced by pituitary injection, and the eggs fertilized in a sperm suspension. These eggs were chosen because they are completely self-sufficient in terms of food; represent a generalized cell type rather than a specialized cell type for a comparatively long period of time during development; are easily tagged; and are readily obtainable in large numbers.

The fertilized eggs are exposed to such drugs as dinitrophenol and allowed to develop to pre-determined stages. Controls from the same clutch, and during the same developmental stages are used for comparison. At the various stages of development, control and experimental eggs and embryos are removed, and the pertinent components extracted, analyzed and compared.

9. PROJECT DESCRIPTION - CONTINUED

Major Findings: The development of standard methods for permitting direct comparison of C^{14} activities between control and experimental eggs and embryos.

In terms of changes in C^{14} during various developmental stages it has been found that C^{14} activity in fats begins to drop soon after cleavage begins, but that C^{14} activity in proteins remains the same for a long period of development. When the eggs are exposed to 0.2% dextrose, the drop in C^{14} activity in the fats is less than that of the controls, while the proteins remain at the same level as the controls, and show no change. When exposed to 1:1,000,000 dilution of dinitrophenol, the C^{14} activity of the fats drops more sharply than the controls, and the C^{14} activity of the proteins shows a sharp decline which is absent in the controls and in the dextrose-treated group. During these developmental stages, there is no apparent decline, in both controls and experimental embryos, in the weights of either the fats or the proteins.

Significance to NIAMD Research: In order to understand the internal responses of cells and tissues to drugs and to stress and thus the effects of drugs and stress on an organism, the changes occurring within the cells and tissues must be thoroughly analyzed. The methods discussed above appear to be able to supplement and extend information obtainable by other physiological, pharmacological, biochemical and physical methods.

Proposed course of project: Further refinements of methods are indicated as well as the isolation and analysis in terms of changes in C^{14} activity of the various amino acids and nucleic acids. The changes in these may indicate the mechanism whereby marked changes in C^{14} activity in proteins occurs without apparent weight change, after exposure to dinitrophenol.

T.P.O. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD- 62129-88
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956	7,700	1		1	1		1	
FY 1956	7,700	1		1	1		1	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD- 62129-83
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Sperling, F. Electron-track autoradiography of radioactive frog embryos. Nature, 174: 749, Oct. 16, 1954.

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Laboratory of Physical Biology
LABORATORY OR BRANCH

3. Physical Biochemistry
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NIAMD- 62130-90
SERIAL NO.

6. The mechanism of the orderly aggregation of proteins in building up biological structures
PROJECT TITLE

7. Dr. Koloman Laki and Dr. R. R. Williams
PRINCIPAL INVESTIGATOR(S)

8.
Dr. W. J. Bowen
Dr. D. R. Kominz
Dr. W. R. Carroll
Dr. H. A. Saroff
Dr. R. B. Simpson
Dr. F. Irreverre
E. R. Adamik
M. J. Callanan
R. L. Evans
E. R. Mitchell
A. R. Hayden
T. D. Kerwin
Farida M. Saad
Margot K. Schumm
S. S. Stone
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objective of this project is to study the mechanism of polymerization of proteins in order to gain insight as to how cells build up network structures. The structures involved in muscular contraction and blood coagulation are the results of protein polymerization. The main part of this project is, therefore, devoted to the study of proteins involved in muscular contraction and blood coagulation.

Methods Employed: The method of attack is both direct and indirect. In the direct attack the proteins of muscular contraction on blood coagulation are separated from their native milieu and are studied under arbitrary conditions which are selected to reveal properties of interest. (Isolation; characterization: size and shape of the molecules; determination of chemical composition; modifications brought about by changing specific groupings either chemically or enzymatically.) In the indirect attack studies are made on some other already better known proteins to

9. PROJECT DESCRIPTION - CONTINUED

gain information before the direct attack is made (e.g. methylation of serum albumin or a study of antigen-antibody reaction). In these studies the procedures of biochemistry and physico-chemistry are employed. For example: paper and ion-exchange chromatography, enzymology, ultracentrifugal analysis, osmometry, light-scattering measurements, electrophoresis, the diffusion measurements, etc.

Major Findings: It was further demonstrated that ATP-splitting and contraction of muscle fibers are not correlated (Bowen) and it was found that besides ATP and ITP, inorganic salts KSCN, KI (known to depolymerize actin), cause muscle fibers and myosin-B threads to contract (Laki, Bowen).

It was observed that both human and bovine serum albumin can be induced to polymerize reversibly under the influence of hydrogen ions and salts (Saroff). Some intrinsic binding constants have been measured in connection with the interaction of proteins and metal ions, and it was shown that copper ions dimerize serum albumin (Saroff, Simpson).

A quantitative determination of the amino acid composition of the two peptide components of co-fibrin has been achieved. It was found that guanidinated fibrinogen is clotted by thrombin and that the co-fibrin released also contains guanidinated amino acids (Laki, Kominz, Saroff).

The presence of the amino acid lysine (with its amino group covered) was discovered in the protein - salmine (Kominz).

Salmine was found to be heterogeneous from the chemical point of view in spite of its homogeneous appearance in physico-chemical measurements (Carroll, Kominz).

It was further demonstrated by using tropomyosin and salmine that O-methyl-iso-urea is a favorable new reagent to detect α-amino end groups in proteins (Saroff, Irreverre, Kominz).

A peptide was found in human γ-globulin preparations which inhibited the agglutinin reaction characteristic for rheumatoid arthritic patients (Williams).

Significance to NIAMD Research: When part of the protoplasm or the whole cell (as in, e.g., cell division or muscular contraction) performs mechanical work, a network structure is built up at least temporarily, mainly through an orderly polymerization of globular proteins. This structure then reacts with the surrounding material and by

9. PROJECT DESCRIPTION - CONTINUED

utilizing metabolic energy (stored in ATP e.g.) performs work (muscular contraction, ameoboid movement). In order to understand this "mechano-chemical coupling" (the interaction of structure with the surrounding) and its disorders, we must know how such structures are built up. Muscular contraction and blood clotting are examples of processes where structures are built up through protein polymerization. Such knowledge eventually will lead us to the understanding of certain diseases of muscle. Study of blood clotting, in addition to supplying clues for protein polymerization, gives us better understanding of the disorders of blood clotting (like hemophilia).

When both direct and indirect approach leads to some specific disease (e.g. hemophilia, rheumatoid arthritis) the advantage offered by studying the disease is utilized to the extent profitable.

Proposed course of project: In the next calendar year the project will be pursued along the lines outlined above. It is further planned that a study on hemophilia will include a study of the clotting defect of a hemophilic patient. The possible physiological role of co-fibrin will be investigated. The partial analysis of the amino acid sequence of one of the peptides of co-fibrin is planned, together with a search for an enzyme which might split off the tyrosine-bound sulfate from the peptide. Physico-chemical studies will be further extended to study the effect of temperature on the two modifications of myosin. The usefulness of O-methyl-iso-urea as an end-group reagent will be further investigated and the agglutinin reaction of rheumatoid patients will be studied further.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD- 62130-90
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	144,300	12	13	25	12	12	24	
FY 1956	147,300	12	13	25	12	13	25	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 10)

Dr. Harold A. Scheraga, Department of Chemistry, Cornell University, Ithaca, New York.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62130-90
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Bowen, W. J., and Kerwin, T. D.: The kinetics of myokinase. I. Studies of the effects of salts and pH and of the state of equilibrium. Arch. Biochem. Biophys., 49: (1) 149-159, Mar., 1954.

Irreverre, F., and Martin, W. L.: Versatile technique of paper chromatography. Anal. Chem., 26: 257, Feb., 1954.

Kominz, D. R., Hough, A., Symonds, P., and Laki, K.: The amino acid composition of actin, myosin, tropomyosin and the meromyosins. Arch. Biochem. Biophys., 50: (1) 148-159, May, 1954.

Laki, K., Kominz, D. R., Symonds, P., Lorand, L., and Seegers, W. H.: The amino acid composition of bovine prothrombin. Arch. Biochem. Biophys., 49: (1), 276-282, Apr., 1954.

Lorand, L. and Laki, K.: A simple method for purifying an activator of prothrombin (antihemophilic factor)? Biochim. Biophys. Acta, 13, 448-449, 1954.

Saroff, H. A.: Diffusion Apparatus. Patent 2675349, Apr. 13, 1954.

Friess, E. T., Morales, M. F., and Bowen, W. J.: Some further observations on the interaction of EDTA with the myosin-ATP system. Arch. Biochem. Biophys., 53: (1) 311-313, Nov., 1954.

Bowen, W. J., and Kerwin, T. D.: A study of the effects of ethylenediamine tetraacetic acid on myosin ATP-ase. J. Biol. Chem., 211: (1) 237-247, Nov., 1954.

Scheraga, H. A., Carroll, W. R., Nims, L. F., Sutton, E., Backus, J. K., and Saunders, J. M.: Hydrodynamic properties of urea-denatured fibrinogen. J. Polymer Sci., 14: (77) 427-442, Nov., 1954.

Laki, K.: The chemistry of prothrombin and some of its reactions. Physiol. Rev., 34: (4) 730-735, Oct., 1954.

Edsall, J. T., Maybury, R. H., Simpson, R. B., and Straesale, R.: Dimerization of serum mercaptalbumin in presence of mercurials. II. Studies with a bifunctional organic mercurial. J. Am. Chem. Soc., 76: 3131 (1954).

16. PUBLICATIONS - CONTINUED

Anfinsen, C. B., Jr., Redfield, R. R., Cloate, W. L., Page, J., and Carroll, W. R.: Studies on the gross structure, cross-linkages, and terminal sequences in ribonuclease. J. Biol. Chem., 207: 201, 1954

Laki, K., and Bowen, W. J.: The contraction of muscle fiber and myosin-B thread in KI and KSCN solutions. To appear in Biochim. Biophys. Acta.

Simpson, R. B., Evans, R. L., and Saroff, H. A.: Polarography of the noble metals. To appear in March 1955 Jour. of Am. Chem. Soc.

Bunim, J. J., Sokoloff, L., Williams, R. R., and Black, R. L.: Rheumatoid arthritis: A review of recent advances in our knowledge concerning its pathology, diagnosis and treatment. To appear in Feb. 1955 issue of Jour. of Chronic Diseases, Vol. 1, No. 2.

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases

2. Clinical Investigations
LABORATORY

3. Arthritis and Rheumatism
BRANCH

4. Bethesda
LOCATION

5. NIAMD - 62131-91
SERIAL NUMBER

6. The Nature of the Anemia of Rheumatoid Arthritis
PROJECT TITLE

7. Franklin G. Ebaugh, Jr., M.D.
PRINCIPAL INVESTIGATOR

8. Ralph E. Paterson, M.D., Gerald P. Rodnan, M.D., Joseph J. Bunim, M.D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To afford an understanding of the reasons why certain patients with active rheumatoid arthritis become anemic.

Methods Employed: The measurement of the duration of circulating erythrocytes life span in patients utilizing the Ashby Selective Agglutination technique and radioactive Sodium Chromate labeled red blood cells: determinations of serum copper and the determination of the rate of plasma iron clearance and the subsequent rate of utilization of iron by the bone marrow to make erythrocytes by radioactive Fe-59 tracer techniques and the chemical determination of the serum iron; the measurement of the rate of excretion in the fedes of urobilinogen and blood serum bilirubin levels; and concurrent clinical studies on the natural course of the anemia and the effect of certain steroids on the course of the anemia.

Patient Material:

		No.	Average Stay Days
Admissions:	Adult males	8	180
	Adult females	14	
	Children male	1	
	Children female	2	
Outpatient:	Number of patients	7	
	Number of visits	21	

Major Findings: The mean red blood life span in a series of patients was determined and found in the majority of patients not to be significantly shortened from a comparable group of normal males and females. The dynamics of iron metabolism were studied in a number

NIAMD - 62131-91 Project Description Sheet Continued

of patients and the rate of hemoglobin production estimated. The serum iron was found to be low in most patients. The administratio of iron orally or intravenously did not significantly increase the serum iron or the red blood cell counts. Thus it is concluded that a deficiency of body iron is not the cause of the anemia. An abnormal type of pyrrole metabolism not previously described has been found to occur in arthritic patients. A new method has been develo for the determination of serum copper.

The beneficial effect of steroid therapy on the anemis of arthritis, described previously by others, has been confirmed, and although the mechanism whereby steroids cogvert the anemia is currently not understood, some progress on this problem has been made by studies presently in progress.

Signigicance to NIAMD Research: This study is but one of several long term projects whose aim is to understand more fully the cause of rheumatoid arthritis and its cure. This project illustrates progress in a clinical and laboratory study of the natu of the anemia of rheumatoid arthritis. It is possibility although b no means a certainty that a more complete understanding of the mech nism of the genesis of anemia of arthritis will lead to clues ultim ely useful in discoveries of the cause of arthritis.

Proposed Course of Project: Studies concerning the mechanism of steroid acti on the anemia will be continued as well as studi designed to more fully characterize the defect in pyrrole metaboli demonstrated in the current studies.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62131-91
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	23,100	2	1	3	1 1/3	1	2 1/3	4500
FY 1956	25,000	2	1	3	2	1	3	4500

12. BUDGET ACTIVITY:

RESEARCH ☒
ADMINISTRATION ☐
REVEIW & APPROVAL ☐
TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62131-91
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Peterson, R.E., and Bollier, M. The Determination of Serum Copper with bis-Cyclohexanone-Oxalyldihydrazone. Anal. Chem., In press

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Clinical Investigations
LABORATORY

3. Arthritis and Rheumatism
BRANCH

4. Bethesda
LOCATION

5. NIAMD-62131-92
SERIAL NUMBER

6. Iron Metabolism in Man, in Health and Disease
PROJECT TITLE

7. R. E. Peterson
PRINCIPAL INVESTIGATOR

8. G. Rodnan; F. Ebaugh; M. Bollier
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objectives of this project are the study of oral iron absorption in patients with liver disease and patients with various anemias, and determination of the turnover rate of iron in the normal male and female, and in patients with various hematological disorders.

Methods Employed: Oral iron absorption is determined by feeding a trace quantity of radioactive ferric salt and determining the per cent absorbed and the per cent incorporated into the red cells. Iron turnover rate is also determined by the use of radioactive iron.

Patient Material:

		No.	Average Stay (Days)
Admissions:	Adult males	12	20
	Adult females	10	20
	Children	0	0
Outpatient:	Number of patients	20	
	Number of visits	120	

Major Findings: Studies to date seem to indicate that patients with liver disease and patients with certain anemias absorb more iron than normal subjects; however, a final evaluation of this data must await additional studies on normal male and female subjects.

The studies on iron turnover rate show an average figure of 0.50 mg/kilo/day in the normal female, and a similar figure for the

9. PROJECT DESCRIPTION - Continued

normal male. However, too few studies with normal males have been made to state that there is no sifnificant sex difference. A series of more than 100 studies have been carried out in patients with various anemias, and it appears that the iron turnover rate is not always directly correlated with the rate of hemoglobin production.

Significance to NIAMD Research: The studies on iron absorption are of significance as related to the problem of the pathogenesis of siderosis (iron storage disease). The studies on iron turnover are directed towards an evaluation of this method as a simple procedure for investigating hemoglobin synthesis *in vivo*.

Proposed Course of Project: Additional studies of iron absorption in normals should be carried out, as a "yardstick" to evaluate the findings in disease. Also, additional iron turnover rate studies must be carried out in normal males. Themethod must also be further evaluated in various disease states.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD-62131-92
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	16,700	1	2	3	1	1 1/6	2 1/6	440
FY 1956	17,000	1	2	3	1	1 1/2	2 1/2	500

12. BUDGET ACTIVITY:

RESEARCH ☒
ADMINISTRATION ☐
REVIEW & APPROVAL ☐
TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

Georgetown University Hospital

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH PROGRAM ACTIVITIES

Honors, Awards, and Publications Sheet

15. NIAMD-62131-92
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases

2. Clinical Investigation
LABORATORY

3. Metabolic Diseases
BRANCH

4. Bethesda
LOCATION

5. NIAMD - 62131-93
SERIAL NUMBER

6. Studies of Purine Metabolism in Gout
PROJECT TITLE

7. James B. Wyngaarden, Stanton Segal, Lenard Laster, and J.E. Seegmiller
PRINCIPAL INVESTIGATORS

8. Lois Liddle and Alberta Blair
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To gain understanding of clinical gout by studying uric acid biosynthesis and excretion in normal and gouty subjects, and by investigating the mechanism of action of drugs which influence these factors.

Methods Employed: The incorporation of isotope from orally administered labeled precursors into various purine excretion products was studied in normal and gouty subjects. Uric acid excretion in patients with various stages of gout, and the effect of drugs on this excretion were investigated. The serum and urin of patients were assayed with enzymatic and chromatographic methods for compounds related to purine metabolism. Pigeon liver homogenates were used for *in vitro* studies of pathways of uric acid biosynthesis.

Major Findings: In confirmation of our previous studies, in a second normal subject 4-amino-5-imidazolecarboxamide-4-C^{13} was again incorporation uric acid by two metabolic pathways and also depressed the incorporation of glycine-N^{15} into uric acid, suggesting an inhibition of the *de novo* synthesis of purines from glycine. An absence of isotope dilution of 4-amino-5-imidazolecarboxamide (AIC) recovered form urine during the study indicated that there is no rapidly miscible pool of this compound in body fluids. The incorporation of AIC into uric acid in one gouty patient studied was greater than normal.

Phenylbutazone, a drug which lowers plasma uric acid levels, was shown to act solely as a uricosuric agent, having no effect on rates of synthesis or of catabolism of uric acid. Antabuse, a xanthine

oxidase inhibitor, was shown to effect only a meager reduction of urate excretion when given in near-toxic doses. Probenecid, another uricosuric agent, was shown to be relatively ineffective when renal damage was severe.

Aliterature report that blood glutamine levels were very low and oxypurine levels very high in gout was not confirmed. Normal subjects on low purine diets were shown to excrete xanthine, hypoxanthine, adenine, guanine and 8-methyl guanine in 0.5 - 10 mg. quantities daily.

Significance to NIAMD Research: We have shown that in the human, as in other b biological systems, AIC is a precursor of uric acid, although its presence as a normal intermediate in purine metabolism has not been demonstrated. This compound can now be used to study clinical conditions involving abnormalities of purine metabolism. The finding that AIC can depress the de novo synthesis of purines in the human suggests new fields of investigation of the factors involved in the regulation of purine production.

The mechanism of action of drugs useful in the treatment of gout has been further elucidated. The role of 7-methyl guanine in purine metabolism is not known and remains to be investigated.

Proposed Course of Project: Studies with labeled AIC will be continued to include a variety of clinical conditions in which hyperuricemia is found. The mechanism by which AIC exerts its effect on purine biosynthesis will be investigated. Methods are being developed for a study of the excretion of possible metabolic precursors of purines in patients with gout. Patients will be investigated for precipitating factors of attacks of acute gout and for variations of uric acid excretion during the course of their disease.

The question of whether or not overproduction of uric acid in gout involves nucleic acid pathways or a more direct route is currently under investigation by means of a study of the time courses of C^{14} enrichment of urinary purines (adenine, guanine, 7-methylguanine, hypoxanthine, xanthine and uric acid) following glycine-1-C^{14} feeding. The validity of equating urinary adenine and guanine enrichment with that of nucleic acids is being evaluated by means of periodic sampling of white cell nubleic acid purine moieties.

Studies of early intermediates in purine synthesis are being continued in pigion liver enzyme systems.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62131-93
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	53,400	4	4 1/2	8½	3 1/3	4½	7 5/6	260
FY 1956	61,000	4	5	9	4	4½	8 ½	300

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PORJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

Section on Intermediary Metabolism, LBN, NIAMD - 62117-

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954 Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62131-93
SERIAL NUMBER

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

The Effect of Phenylbutazone on Uric Acid Metabolism in Two Normal Subjects, James B. Wyngaarden. J. Clin. Investigation. In Press.

Uric Acid. James B. Wyngaarden, in G.M. Piersol, Cyclopedia of Medicine, Sugery, and Specialities, F.A. Davis and Co. Philadelphia, In Press.

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Clinical Investigations 6
LABORATORY

3. Arthritis and Rheumatism
BRANCH

4. Bethesda
LOCATION

5. NIAMD-62131-94
SERIAL NUMBER

6. Studies on New Antirheumatic Steroids
PROJECT TITLE

7. Joseph J. Bunim; Alfred J. Bollet; Roger Black
PRINCIPAL INVESTIGATORS

8. NONE
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The great inadequacy of present methods of treatment of rheumatoid arthritis has resulted in a search for new drugs which might be of therapeutic value. In view of the useful, though inadequate, effect of steroids that are now in use, other steroid compounds are being sought which might have greater value. The present study seeks to determine if new steroids which have been synthesized have greater therapeutic usefullness by reason of greater anti-rheumatic potency with fewer side-effects.

Methods Employed: Studies have been in progress at NIAMD concerning two new steroids, metacortandralone and metacortandracin, synthesized by the Schering Corporation. The effect of these drugs in rheumatoid arthritis has been evaluated by administering them to patients, after suitable control observations, and carefully noting changes in symptoms, joint changes, functional capacity, tissue pathology, and blood constituents. The symptomatic changes are recorded after careful questioning of the patient. Joint changes are noted by careful examination of every joint, recording each type of finding by means of a numerical code, and then quantitating the severity of these changes my means of this code. The functional state of each patient is observed by means of a careful measurement of the range of motion of each joint, expressing the total abnormality in range of motion as a percentage of normal. Tissue changes are observed by means of biopsies of synovial or other tissues. Changes in the ESR, C-Reactive protein, serum proteins, serum electrolytes, cholesterol, calcium, phosphorus, hemoglobin, white blood cells and circulating eosinophiles are also checked. Hormonal effects of these drugs are observed by means of the above tests, plus observations on excretion of 17-keto-steroids.

9. PROJECT DESCRIPTION - Continued

Studies in progress include the effectiveness of these drugs in rheumatoid arthritis, both on a short-term basis and as long-term therapy. Careful metabolic balance studies are being conducted to observe the effect of the drugs on electrolyte, nitrogen, calcium, phosphorus and water metabolism. Pharmacologic studies of the rate of disappearance of these steroids from the blood and excretion in the urine are under way; and, studies of their clinical effectiveness in other rheumatic diseases, especially lupus erythematosus.

Major Findings: Results thus far have indicated that these drugs have potent antirheumatic and anti-inflammatory effects, several times more potent than cortisone and hydrocortisone. Patients experience dramatic relief of pain, increase in functional capacity, subsidence of the manifestations of joint inflammation, with marked clearing of the acute inflammatory changes in the tissues and changes in the serum abnormalities. In addition the drugs have been observed to have potent adrenal hormone actions, inducing eosinopenia and fall in excretion of 17-ketosteroids. They also induce a fall in serum globulin and a rise in serum cholesterol. These drugs did not cause salt and water retention, one of the main side effects of cortisone. They do cause a loss of nitrogen, but this is not as great as with previous steroids.

Minor side-effects have been observed with these drugs, including hirsutism, amenorrhea, moon-face, acne, abdominal discomfort, and some mental clouding. No serious side-effectsdefinitely attributable to these drugs has been observed as yet. Some tendency for the effectiveness of the drug to diminish after prlonged administration has been noted, but this has not been observed sufficiently to determine how seriously it will impair the usefullness of the drugs.

Significance to NIAMD Research: This study has given reason to hope for significant advances in the treatment of rheumatoid arthritis and other rheumatic diseases in the near future. The drugs currently under investigation have been found to be potent agents, without some of the serious side-effects of previous steroids. Their final value and place in the treatment of the rheumatic diseases remains to be worked out, but it seems certain that they will be of some importance. These results also give encouragement that similar modifications of the basic steroids will result in more useful drugs.

Proposed Course of Project: It is planned tocontinue the present line of investigation of these new steroids in order to determine what their effectiveness is and what role they may play in the treatment of rheumatoid arthritis and the other rheumatic diseases. Specifically, the problem of adequate dosage and treatment schedules is being worked out, side-effects are being carefully noted and means of avoiding them studied, the development of resistance to the effects of the drug is being carefully investigated. Similar studies are under way in lupus erythematosus and scleroderma and these will be enlarged, and repeated with other rheumatic diseases.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD-62131-94
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	21,300	2	½	2½	1 5/6	½	2 1/3	1200
FY 1956	22,000	2	1	3	2	½	2 ½	1200

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

Dr. Maurice Pechet - National Heart Institute

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD-62131-94
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Observations on the Anti-Rheumatic Potency, Metabolic Effects and Hormonal Properties of New Synthetic Steroids, Metacortandralone and Metacortandracin. Presented at ARA Meeting 11/4/54 and in Press J.A.M.A.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Clinical Investigations
LABORATORY

3. Arthritis and Rheumatism
BRANCH

4. Bethesda
LOCATION

5. NIAMD - 62131-95
SERIAL NUMBER

6. Studies of Mucopohpacchasides and other Components of Connective tissues in Rheumatic and other Diseases, and of similar Components in Blood, Urine and Synovial Fluid.
PROJECT TITLE

7. Alfred Jay Bottet, Norman Boas
PRINCIPAL INVESTIGATORS

8. Joseph Foley, Mary B. Gospodaek
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To investigate alterations of mucopolysaccharide structure and of hexosamine metabolism in response to various pathological states.

Methods Employed: The biosynthesis of hexosamine has been studied both in intac rats on a hexosamine free diet and *in vitro* using fragments of rabbit connective tissue grown in tissue culture. The effect of thyroidectomy and hypophysectomy on the concentration of hexosamine in rat plasma and connective tissue has been investigated. Paper electrophoresis has been used to separate components of normal connective tissue and the hexosamine content of various fractions were the determined. In human studies the effect of scleroderma on the hexosamine content of connective tissue has been studied and the effect of stress, ACTH administration and various pathological states on concentration of hexosamine in blood and urine has been investigated.

The intrinsic viscosity of synovial fluid from patients with various rheumatic diseases has been determined as part of a study of abnormalities of hyaluronic acid in pathological states.

Major Findings: The major findings of these studies include the observation that the intact animal suffers no loss of carcass hexosamine a hexosamine-free diet, that rabbit connective tissue can synthesize hexosamine *in vitro*, that thyroidectomy and hypophysectomy cause changes in connective tissue and blood hexosamine levels (thyroidecto raising the levels and hypophysectomy preventinh the effect of thyroidectomy). Serum proteins were found in abundance in blood -free extracts of connective tissue, and the hexosamine in connective tissue was found to be divided between protein and mucopolysaccharide components of connective tissue about equally. The hexosamine and water content of the skin and subcutaneous tissues of patients with sclero-

derma were found to be raised compared to normal controls. The excretion of hexosamine in the urine was found to be exceedingly constant in normal individuals on a day-to-day basis, and this level was found to become elevated by clinical stress of any type, without any relation to the kind of disease process. ACTH did not cause an elevation in serum or urinary hexoasmine, ruling out the adrenals as the mediator in this response. The hyaluronic acid of the synovial fluid of patients with rheumatoid arthritis was found to be depolymerized compared to normals and to patients with other rheumatic diseases; this depolymerization was not related to the degree of inflammation of the joint, the duration, stage or severity of the arthritis, the degree of cartilage destruction as determined radiologically, and was not reversed by any type of steroid therapy in spit of marked subsidence of the inflammatory reaction as a result of therapy.

Significance to NIAMD Research: These studies throw light upon basic aspect of connective tissue metabolism and physiology in health and disease, giving us information concerning the nature of the synthetic activityies of connective tissue, how these processes are controlled by hormones and why changes appear during endocrine diseases. They also give information concerning the nature of some of the changes observed in disease processes, and may lead to a better understanding of the pathogenesis of certain rheumatic diseases, especially rheumatiod arthritis. New techniques have been devised during the course of these studies, which may help provide more information along these lines.

Proposed Course of Project: At the present time studies are continuing on the nature of the hyaluronic acid in synovial fluid in different diseases, in an attempt to determine the mechanism bringing about the changes observed, and the sighificance of these changes. A search is being made for a possible enzyme which might depolymerize the hyaluronic acid in synovial fluid, to see if changes in the acitvity of such an enzyme could be responsible for the abnormalities observed. The fact that synovial fluid hyaluronic acid is linked in a complex to protein has been demonstrated recently by means of the analytical ultracertrifuge, and studies are commencing concerning the nature of this proteink the amount of it linked to the hyaluronic acid in various joint diseases, and what relation it plays to the observed changes in the mucopolysaccharide. It is also planned to study the synthesis of hyaluronic acid by connective tissue by means of the tissue culture technique devesed earlier.

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62131-95
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	21,300	1	2½	3½	1	2½	3½	210
FY 1956	27,000	2	3	5	2	2½	4½	300

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62131-95
SERIAL NUMBER

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Aynthesis of Hexosamine by Connective tissue (in vitro) Science 120: 1954
Bottet, Boas and Bunim

Effects of Growth, Fasting, and Trauma on Concentration of Connective Tissue Hexosamine and Water. Boas and Foley. P.S.E.B.M. 1954

Regulation of Connective tissue Hexosamine Levels by the Anterior Pituitary and Thyroid Glands. Boas and Foley. P.S.E.B.M. 1954

Effect of Thyroidectomy and Hypophysectomy on Plasma Hexososamine Level and the rate. Boas and Foley. Endocrinology. (in press)

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Clinical Investigations
LABORATORY

3. Arthritis and Rheumatism
BRANCH

4. Bethesda
LOCATION

5. NIAMD - 62131-96
SERIAL NUMBER

6. Physiological, Pharmacological and Enzymological Studies on Corticotropin, Cortisone, Hydrocortisone, Radioactive Hydrocortisone.
PROJECT TITLE

7. R.E. Peterson, J.B. Wyngaarden, K.J. Isselbacher and J.J. Bunim
PRINCIPAL INVESTIGATORS

8. Charles Pierce, Margaret Bollier, and P. Michael
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The following are the main objectives of this project: 1) Pharmacology and physiological disposition of hydrocortisone, cortisone, and corticosterone in man and animals. 2) Metabolic transformations of hydrocortisone, cortisone, and corticosterone in man *in vivo*, and *in vitro*, and the enzyme systems involved in the latter. 3) The turnover rate of endogenous hydrocortisone in man, and 4) the development of new methods for the determination of the corticosteroids and their metabolites in biological fluids.

Methods Employed: Pharmacological quantities of pure steroids and steroids labeled with Carbon-14 have been used to carry out many of these studies. Imporved methods have been devised for the assay of steroids in micro quantities. Standard techniques have been used for the Carbon-14 assay work, and the work in the enzymology field.

Major Findings: In studies of the disposition of radiometabolites of hydrocortisone-4-C^{14} in rats and guinea pigs, it was shown that 83 per cent of the products were excreted in bile of rats in 3 hours whereas only 15 per cent appeared in the bile of guinea pigs in 3 hours, though 65 per cent appeared in bile eventually in this species. The feces were the cheif route of excretion in the rat, whereas the urine was the chief route in guinea pigs. In both species enterohepatic circulation of labeled metabolites occurred. In neither species was the expired CO$_2$ labeled. The labeled substances were excreted in conjugated form.

Studies on disposition of hydrocortisone and cortisone in man have shown no difference in the rate of metabolic transformation of

trace and pharmacological quantities. A very rapid and complete metabolism of these two steroids has been shown - over 98 per cent of an injected dose is metabolized in a normal person and one-half of these metabolites appear in the urine in 3 to 4 hours. More than 80 per cent is excreted in the urine in 24 hours, and more than 90 per cent has appeared by the end of 72 hours. Four per cent can be accounted for by fecal excretion. Practically no enterohepatic circulation exists, since studies in a bile fistula man have shown only 4 per cent excretion via this route. Studies on the rate of disappearence of hydrocortisone from the plasma have demonstrated in normal subjects that 50 per cent disappears in two hours: however, in liver disease the steroid is metabolized much slower. In hyperthyroidism the steroid is metabolized more rapidly. Comparative studies with steroids structurally similar to hydrocortisone have shown that these steroids are metabolized more rapidly than gydrocortisone, and also that liver dysfunction does not impair their rates of metabolism.

A procedure has been developed for measuring the miscible pool of endogenous hydrocortisone, and its rate of turnover. Since hydrocortisone-4-C^{14} when injected intravenously in trace quantities disappears exponentially with time, it is possible to derive turnover data by calculating the hydrocortisone specific activity at various times following injection . Preliminary results suggest that the pool in a normal subject is 3 to 4 mg. and that this pool is turned over approzimately 10 times per day.

Mechanism of Inactivation and Excretion of Adrenal Steroids

A. Enzymes have been isolated form animal liver which convert adrenal steroids to their inactive "tetrahydro" form. Two enzyme systems seem to be involved in this process of adding 4 hydrogen atoms to the steroid. The enzymes have been purified 150 fold and their properties and cofactors defined. This seems to be a general mechnism for steroid inactivation.

B. The manner in which the reduced or tetrhydro corticosteroids are subsequently conjugated as their glucuronides has been under study. The formation of the Glucuronide serves to assist in the excretion of steroids in the urine by making them water soluble. It has been Observed that an "active glucuronide donor" is necessary. This has been found to be a substance, uridine diphosphate glucuronic acid. This cofactor is found in liver and with the aid of an enzyme in the microsomes of liver transfers its glucuronic acid to the steroid.

Purification of the enzyme and studies as to its specificity are under investigation. However, it is apparent that uridine diphosphate hlucuronic acid serves as a cofactor in the formation of many other glucuronides as well.

A new much more selective method for the determination of the urinary 17-ketosteroids has been developed. Studies are underway directed towards improvements in the methods for assay of the urinary

corticosteroids, especially in regard to improvements in the procedure for their hydrolysis. Various imporvements intthe methods in use for determination of the plasma steroids have been developed. This has been related to both the phenylhydrazine method, and the sulfuric acid-ethanol fluorescent method.

Significance to NIAMD Research: The studies on physiological disposition and pharmacology are important in regards to the treatment of patients with steroids. The studies on *in vivo* and *in vitro* metabolism are hoped to yield information relating to steroid actions in biological systems. The studies on turnover rate should make it possible for the first time to determine the actual production of hydrocortisone by the adrenals in various disease states and in normal subjects. The studies on methodology are necessary to make it possible to more reliable carry out all of these studies.

Proposed Course of Project: Additional data are needed on the disposition and pharmacology of corticosterone, and other newer steroids analogs showing therapeutic promise. Studies on the *in vitr* metabolism will be directed towards the enzyme systems involved in the conjugation of the steroid metabolites, and heretofore undescrib enzyme systems involved in steroid biotransformations, and systems directed towards the synthesis of steroids *in vivo*. Studies on the *in vivo* biotransformation products of the steroids will be carried out. A great deal of effort will be directed towards the studies of hydrocortisone turnover rate in normals and in disease states. Further work will be carried out on better methods for the hydrolysis and determination of the metabolites of the steroids in biological fluids.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIMAD - 62131-96
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	49,800	3	4	7	3	3 1/3	6 1/3	1000
FY 1956	56,000	3	5	8	3	5	8	1200

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

Dr. Brodie, National Heart Institute

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OR PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62131-96
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Wyngaarden, J.B., Wolff, A., and Peterson, R.E. Disposition of Hydrocortisone-4-C^{14} in the Rat. J.B. C., In press

17. LIST HONORS AND AWARDS RELATING TO THIS PROJECT AND THE PERSONNEL DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Arthritis and Rheumatism
LABORATORY

3. Diaeases of the Blood
BRANCH

4. Bethesda
LOCATION

5. NIAMD - 62131-97
SERIAL NUMBER

6. The dynamics of red blood cell destruction and production in various types of anemia, normal males and females, and various laboratory animals.
PROJECT TITLE

7. Franklin G. Ebaugh, Jr., M.D.
PRINCIPAL INVESTIGATOR

8. Gerald P. Rodnan, M.D.
OTHER INVESTIGATOR

9. PROJECT DESCRIPTION

Objectives: To develop a practical new technique for measuring rates of red blood cell destruction in a variety of anemic states and in normal man and animals, to establish normal values of red blood cell destruction in healthy male and female, and a number of animals, and to delineate the nature of anemia in hypothyroid states and iron deficiency anemia.

Methods Employed: Measurement of red blood survival in vivo by means of radioactive sodium chromate labeled red cells and Ashby Selective Agglutination and iron metabolism by radioactive Fe-59 tracer techniques and the chemical determination of the serum iron employed together with concurrent clinical studies.

Major Findings: Simultaneous employment of the radioactive sodium chromate technique and Ashby Selective Agglutination for measuring the life span of circulating red blood cells in vivo in normals as well as a wide variety of anemias with normal and abnormal hemoglobins have led to further information on the rate of elution of sodium chromate from circulating red blood cells in vivo. The duration of red blood cells survival in normal females and males has been confirmed by the radioactive sodium chromate technique. The life span of the red blood cells in the chicken, pigeon, and rat has been determined.

Significance to NIAMD Research: These studies illustrate progress in the search for and development of a practical, safe, and reliable method for measuring red blood life span in humans and animals which eliminates the risk and practical limitations inherent in current widely used immunologic techniques for studying rates of red blood

cell destruction. The rates of elution of sodium chromate from normal and a wide variety of diseased red blood cells is impractical for establishing the limits of usefulness and interpretation of results obtained with this new method of measuring red blood cell survival. The rates of red blood destruction determined in normal females and males are essential as a standard of comparison for findings in various diseased states. The lenght of survival in a wide variety of laboratory animals will be of fundamental histologic importance to the comparative physiologist and to studies of expermentally induced anemia in laboratory animals. It is hoped that studied on the anemia of hypothyroidism and iron deficiency anemia will lead to a more complete understanding of the geresis of the anemia in these metabolic disorders.

Proposed Course of the Project: It is planned to expand the number and types of hemolytic syndromes studied with radioactive sodium chromate and further characterize the advantages and limitations of this new method. The type and number of normal laboratory animals studied will be expanded.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62131-97
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	10,100	2/3	1 1/3	2	2/3	.5/6	1 ½	4500
FY 1956	14,000	1	2	3	2/3	1 1/3	2	4500

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVEIW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62131-97

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Clinical Investigations
LABORATORY

3. Metabolic Diseases
BRANCH

4. Bethesda
LOCATION

5. NIAMD-62131-98
SERIAL NUMBER

6. Studies in diabetes mellitus
PROJECT TITLE

7. J. B. Field
PRINCIPAL INVESTIGATOR

8. DeWitt Stetten; D. Jermany
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To study the relationship of dietary carbohydrate and fat to ketonuria in normal and diabetic subjects. To further study the mechanism of hypoglycemic unresponsiveness in cases if islet cell adenoma of the pancreas. To determine the presence of humoral insulin antagonists in cases of insulin resistance, ketosis and infections complicating diabetes.

Methods Employed: Diabetics were given isocaloric diets with variations in the percentage of fat and carbohydrate. The effects of these alterations on ketonuria, insulinrequirement, and presence of diabetic complications were observed.

Liver biopsies from patients with islet cell adenomas of the pancreas were analyzed for the amount and type of glycogen present. Similar experiments were carried out in rats who had been treated with insulin.

The ability of the rat hemi-diaphragm to increase glycogen deposition under the influence of insulin is being used as a test system for humoral insul antagonists. Serum from suitable clinical cases will be tested.

Patient Material:

	No.	Average Stay (Days)
Adult males	4	57
Adult females	7	46
Child males	1	56

9. PROJECT DESCRIPTION - Continued

Major Findings: As a result of the dietary study it was shown that dietary constituents influence ketone metabolism primarily by effects on hepatic ketogenesis. High fat intakes do not cause increased ketonuria in the well regulated diabetic, but may be dangerous in the labile diabetic. In the latter, high carbohydrate diets are of great therapeutic value. No relationship was found between the degenerative complications of diabetes and the pattern of ketonuria in response to changes in diet.

Studies on the hypoglycemic unresponsiveness seen in patients with islet cell adenomas seem to indicate that this phenomenom is related to a failure of glycogenolysis in the liver.

The test system involved in measuring insulin effect has been worked out.

Significance to NIAMD Research: The dietary study provides important information on the relationship of isocaloric alterations in diets to the metabolism of ketone bodies and control of the diabetes.

The studies on hypoglycemic unresponsiveness indicate the possible existence of an abnormality in the liver glycogen in patients with islet cell adenomas.

If humoral insulin antagonists are found, they might provide an explanation for the phenomenom of insulin resistance during the course of acidosis and infections in diabetics.

Proposed Course of Project: The serum of insulin resistant diabetics and those with infection and acidosis will be studied to determine if they contain humoral insulin antagonists. If such a factor is found, attempts will be made to further characterize it.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD-62131-98
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	4,900	1	1	2	1/3	$\frac{1}{2}$	5/6	606
FY 1956	8,900	1	1	2	1	$\frac{1}{2}$	$1\frac{1}{2}$	700

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD-62131-98
SERIAL NUMBER

---

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

---

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Clinical Investigations
LABORATORY

3. Energy and Mineral Metabolism
BRANCH

4. Bethesda
LOCATION

5. NIAMD - 62131-99
SERIAL NUMBER

6. Study of the Composition of Local Body Areas in Man
PROJECT TITLE

7. P. Marks, L. Hershemon
PRINCIPAL INVESTIGATORS

8. E. Marsden, Dorothy Anderson
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To develop further a technique for the *in vivo* study of the composition of localized body areas as regards plasma, red blood cells and other constituents, and to study the effect on this composition of various disease states and therapeutic agents.

Methods Employed: Isotope delution techniques, venous catheterization and techniques for the measurement of blood flow in various ogran

Patient Material: (1954 calendar year)

Clinical Center Admissions:	No. of Pts.	Average Stay Days
Adult Males	5	4
Adult Females	3	4
Child Males	0	0
Child Females	0	0
Mt. Alto Hospital	5	4
Georgetown University Hospital	7	4

Major Findings: A new technique has been further developed and applied to the quantitative measurement of plasma and red cell volumes of the splanchnic area in humans. It has been found that the amount of blood in the splanchnic area is sufficient to make it an important blood reservoir. The distribution of plasma and red cells in the splanchnic, pulmonary and total body areas has been characterized.

Significance to NIAMD Research: This method provides an approach to the study of the composition of local areas of the body in terms of various blood and extravascular components. It will aid in defining the alterations which occur in these constituents in various states, eg., arthritis, diabetes mellitus etc.

Proposed Course of Project: An expansion of the studies is planned whereby the effect of various disease states, such as rheumatiod arthritis, myxedema and diabetes mellitus, diseases known to be associated with alterations in total body composition, will be studied in an effort to define the changes occurring in a local area such as the splanchnic bed. In assition to the definition of these changes, the effects of various theropeutic agents will be investigated.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62131-99
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	13,900	1	2	3	5/6	1 1/6	2	32
FY 1956	17,900	1	2	3	1	2	3	100

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACITLITES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62131-99
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Clinical Investigations
LABORATORY

3. Metabolic Diseases
BRANCH

4. Bethesda
LOCATION

5. NIAMD-62131-100
SERIAL NUMBER

6. Studies related to thyroid function and disease
PROJECT TITLE

7. Dr. Paul A. Marks; Dr. Jacob Robbins; Dr. James B. Wyngaarden
PRINCIPAL INVESTIGATORS

8. Dr. Lee Hershenson; Miss Dorothea Jermany
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives:

A. To study the hepatic removal of serum protein-bound iodine in normal and abnormal states.

B. To study the mechanism of creatinuria and the metabolism of water and electrolytes in myxedema.

C. To determine the characteristics of protein binding of thyroid hormone in serum and other body fluids in normal and abnormal states.

D. To delineate the abnnormalities in thyroid metabolism in patients with hypothyroidism associate with goiter.

E. To study iodine metabolism in thyroid homogenates.

Methods Employed: A number of separate techniques have been used in the above studies and include: hepatic catheterization in humans, metabolic balance determinations, reval clearances, zone electrophoresis chromatography. Radioactive iodine has been used as a label in chemical studies, and in studying iodine metabolism *in vivo*.

Patient Material:

	No.	Average Stay (Days)
Adult males	7	4 (Hepatic catheterization study. Five of the 9 patients were admitted to Georgetown Unv. Hosp.)
Adult females	2	

9. PROJECT DESCRIPTION - Continued

	No.	Average Stay (Days)
Adult females	4	75 (Studies on myxedemi

Major Findings: A. The normal liver is capable of removing a large amount of the protein-bound iodine circulating through it, as determined by comparison of arterial and hepatic venous blood.

B. Thyroid homogenates, studied at 4°C, have the ability to utilize iodide, converting it to monoiodotyrosine and, especially, to an intermediate iodine form which is extractable by carbon disulfide.

C. Techniques for use in the other studies have been established

Significance to NIAMD Research: These studies represent new approaches to several aspects of thyroid physiology and disease. These include the mechanism of hormone synthesis in the normal and diseases thyroid, the role of the liver in thyroid hormone metabolism, and the role of the specific thyroxine-binding protein in thyroid physiology.

Proposed Course of Project: The techniques which have been developed will be used to pursue further the problem listed above.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Gudget Data Sheet

10. NIAMD-62132-100
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	34,800	3	3	6	2 ½	2 5/6	5 1/3	336
FY 1956	40,800	4	3	7	4	3	7	400

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

Dr. M. Sherer, NCI-
Dr. J. B. Stanbury, Mass. Gen. Hosp., Boston
Georgetown University Hospital

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD-62131-100
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Wyngaarden, J. B., and J. B. Stanbury. Formation of monoiodotyrosine and an intermediate iodine complex by thyroid homogenates. J. Biol. Chem., Jan. 1955.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

A.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Clinical Investigations
LABORATORY

3. Energy and Mineral Metabolism
BRANCH

4. Bethesda
LOCATION

5. NIAMD - 62131-101
SERIAL NUMBER

6. Studies of the effects of parathyroid hormone and of diet on calcium and phosphe orus metabolism in man.
PROJECT TITLE

7. Howard H. Hiatt and David D. Thompson
PRINCIPAL INVESTIGATORS

8. G. D. Whedon
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objectives of this project are to elucidate the effects of the parathyroid hormone on calcium and phosphorus metabolism in the normal subject and in patients with disturbances of mineral metabolism and to study the factors regulating the activity of the parathyroid gland in normal subjects an in those with disease.

Methods Employed: The renal clarances of calsium and phosphorus are studied before and after the administration of parathyroid hormone and under the influence of several dietary levels of calcuim and phosphorus. The relationship of dietary calcuim to phosphorus stora and of dietary phopphorus to calcium storage are being studied in normal subjects and in patients with destrubances of parathyroid activity by metabolic balance techniques. In addition, the effect of calcium on the cellular transfer of phosphorus are being studied in vitro using isotopes.

Patient Material:

	No.	Average Stay Days
Adult males	8	56
Adult females	7	42
Children male	0	
Children female	1	3
Out patients	1	(Number of visits) 2

Major Findings: The capacity of parathyroid hormone to alter renal tubular function has been demonstrated. A relationship between dietary calcium and phosphours and the reabsorptine capacity of the kidney

tubule for phosphorus has been found in normal subjects. Preliminary studies on the role of the parathyroid glands in this relationship have been carried out.

Significance to NIAMD Research: The diagnosis of disease of the parathyroid glands is hindered by the abence of specific tests of parathyroid function. This is particularly important in patients who have bone disease of absane etiology and in those who repeatedly form renal calculi. The diagnosis and removal of parathyroid tumors in many such patients lead to permanent cure. It is hoped that information obtained in the present studies may lead to more specific methods of diagnosis in such patients. In addition, an attempt will be made to elucidate the function of the parathyroid glands in patients with such diseases of bone as osteoporosis and osteomalacia.

Proposed Course of Project: The studies in normal subjects will be continued. In addition these methods will be employed in the investigation of patients with bone disease, with renal stones, and with known or spspected disorders of parathyroid function. An attempt will be made to determine the rate of endogenous parathyroid hormone secretion under normal acid abnormal conditions. Finally, the mechanism of action of parathyroid hormone will be investigated in contemplated *in vitro* studies.

A.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62131-101

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	37,400	2	3½	5½	1 2/3	3 ½	5 1/6	745
FY 1956	41,400	2	4	6	2	4	6	300

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS,) IDENTIFY SUCH RESEARCH : (BY SERIAL NO. (S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62131-101
SERIAL NUMBER

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Clinical Investigations
LABORATORY

3. Energy & Mineral Metabolism
BRANCH

4. Bethesda
LOCATION

5. NIAMD-62131-102
SERIAL NUMBER

6. Effects of diet and steroid hormones on mineral metabolism in patients with bone disease.
PROJECT TITLE

7. G. D. Whedon; H. H. Hiatt
PRINCIPAL INVESTIGATORS

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To investigate the practical aspects of therapy with diet and steroid hormones of various types of demineralizing bone disease. This involves study of the metabolic effectiveness for mineral storage of oral steroid preparations, their effective dosage levels, and the relationship of the latter to masculinizing or feminizing side-effects.

Methods Employed: Metabolic balance determinations, vaginal smear staining techniques.

Patient Material:

	No.	Average Stay (Days)
Adult Female	1	248
Children female	1	22

Major Findings: In the single female patient with osteoporosis studied over the extended period necessary, the effectiveness was demonstrated of oral androgen and estrogen in promoting the storage of bone salts and protein. Significant masculinizing side-effects did not occur.

Significance to NIAMD Research: Demineralization of the skeleton is a common accompaniment at all ages, ancluding rheumatoid arthritis. Although the value of the steroid hormones administered parenterally has been demonstrated, therapy by this route has usually been abandoned after a brief trial due to inconvenience. If a practical regimen for the necessarily long period (months) of hormone administration in treatment of these bone disorders can be developed from the demonstration of effectiveness of the oral route, a valuable aid to the chronic care of many patients will be provided.

9. PROJECT DESCRIPTION - Continued

Proposed Course of Project: Several additional patients will need to be studied by the metabolic balance technique to prove the effectiveness of oral steroid hormones. The studies will include efforts to define more closely the effective dosage levels and to determine to what extent androgens and estrogens neutralize one another's side-effects while supplementing one another's metabolic effects.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD-62131-102
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	16,700	1	2	3	1	1 1/3	2 1/3	270
FY 1956	19,700	1	2	3	1	2	3	300

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD-62131-102
SERIAL NUMBER

9
16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Nationsl Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Clinical Investigations
LABORATORY

3. Energy and Mineral Metabolism
BRANCH

4. Bethesda
LOCATION

5. NIAMD - 62131-103
SERIAL NUMBER

6. Total energy metabolism; studies in health and disease
PROJECT TITLE

7. G.D. Whedon
PRINCIPAL INVESTIGATOR

8. Ernest E. Huber, Jr.,
OTHER INVESTIGATOR

9. PROJECT DESCRIPTION

Objectives: 1) To establish by complete actual measurement a technique of tot energy balance which can be applied to various clinical problems and to fundamental physiological problems of energy metabolism not now understood; 2) To study the influence on total energy consumpti and balance of various factors, including climate and the endocrine hormones; 3) To investigate the characteristics of energy balance and their influence on the nutritional state of patients in pertian disease conditions, such as obesity and cancer.

Methods Employed: Indirect human calorimetry by means of expired air analysis in the respiratory chamber, metabolic balance determination caloric analysis of dietary intake and of excreta.

Major Findings: During the past calendar year the shell of the respiratory chamber has been assembled, and the installation and testing of the air-conditioning apparatus has been partially completed. Analygers, recorders, meters and pumps are being assembled and tested.

Significance To NIAMD Research: Studies of total energy metabolism have virtually not been carried out previously. All present figures for the daily caloric requirement in various occupations are based either on food consumption data or on brief measurements of activity metabolism extropolated to twenty-four hours. The respiratory chamber, therefor, over long periods of time, in making possible exact measurement total calories expended, is a unique facility

As an example of the type of problem that can be approached in a new way with the chamber is the condition obesity or overweight, which predispones individuals to the development of diabetes, heart disease, and possible high blood pressure and artherioselersis.

It may be possible for the first time to determine whether or not an intrinsic metabolic difference exists between light-eating , fat and heavy-eating, thin individuals. This information might lead the way toward development of effective treatment or prevention of his serious affliction.

Proposed Course of Project: Work will be began this year with normal healthy individuals a) in delineating the patterns of energy expenditure in certain common activities of daily living and b) in establishing the technique of energy balance. When these techniqu are well extablished, clinical studies will follow.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62131-103
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	9,100	1	1	2	1/3	1	1 1/3	-
FY 1956	12,100	1	1	2	1	1	2	-

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH : (BY SERIAL NO. (S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62131-103
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FORM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arhtritis and Metabolic Diseases
INSTITUTE

2. Energy Mineral Metabolism Branch
LABORATORY

3. -
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62131-104
SERIAL NUMBER

6. Studies on Carbohydrate Metabolism
PROJECT TITLE

7. P.A. Marlis and H.H. Heath
PRINCIPAL INVESTIGATORS

8. E. Marsden and D.Graves
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: Elucidation of mechanisms of glucose utlization and glycogen formaliar.

Methods Employed: In vivo and in vibro studies have been carried out with rats and rat liver tissues. In addition, purified enzymes fr various sources have been used to study the mechanism of reaction involved. Synthesis of certain intermediates, degredation of reacti products and radioactive assay of products from studies with labelled precursors have been employed.

Major Findings: 1) Evidence for a series of reactions involing ribose phospha which leads to formation of glucose 6-phosphate with pruified enzymes, transketolase and transaldolase. 2) An effect of diet on the mechanism of glycogin synthesis in rat liver has been demonstrated. 3) Evidence for alternate pathways of glucore utilization in rat liver has been accumulated. 4) Evidence for an important role of erythrose in carbohydrate metabolism has been found.

Significance to NIAMD Research: Elucidation of mechanisms of glucose utilizati and glycogen synthesis are fundemental to our understanding of 1) sources of energy in the body, 2) the possible alterations in normal pathways under various conditions of stress and disease and 3) mechanism by which certain agents may effect gluc utilization.

Proposed Course of Project: Continue efforts to elucidate mechanism of glucose utilization in various mammaliar tissues with particular reference to the possible significance of the oxidative pathways of glucose metabolism.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62131-104
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	11,600	1	1	2	2/3	1	1 2/3	--
FY 1956	14,900	1	1	2	1	1	2	--

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62131-104
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institue of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition LABORATORY	3. Biochemistry and Physiology of Nutrition SECTION
4. Bethesda LOCATION	5. NIAMD - 62113-105. SERIAL NUMBER

6. Nitrogen balance in normal adults on modified Kempner rice-fruit diet, effect of amino acid supplements.
PROJECT TITLE

7. Harold R. Sandstead and James M. Hundley
PRINCIPAL INVESTIGATORS

8. Donald G. Whedon
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To determine whether the nutritive value of rice may be imporved by the addition of amino acids.

Methods Employed: (1) Measurement of nitrogen efficiency by determination of nitrogen balance on constant non-supplemented and amino acid supplemented rice-fruit diets (2800 calories, 26 gm. of protein daily from 250 gm. rice, plus fruit and sugar.)
(2) Measurement of amino acids in plasma and urine on the above dietary regimen.

Patient Material: (1954 Calendar Year)

	No.	Average Stay Days
Admissions: Adult males (normal	3	100

Major Findings: (1) The data suggests that lysine and threonine favored the attainment of nitrogen equilibrium in two of three normal males, but the changes were small and of doubtful significance.
(2) Methionine was not additive to the effect of lysine and threonin

Significance to NIAMD Research: This is an attempt to (1) eliminate some of the undsirable features of a therapeutically useful diet, e.g., the sustained negative nitrogen balance of the rice-fruit diet, and (2) imporve a staple food.

Proposed Course of Project: An extension of the project is planned whereby two or three normal subjects are maintained on

similar rice-fruit diets providing 45 calories per kilo of body weight with the supplementation of amino acids to further elucidate the effect of amino acids on nitrogen efficiency and to differentiate between a specific amino acid effect and the simple provision of dietary nitrogen.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD - 62113-105
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	20,300	1 1/3	2/3	2	1 1/3	2/3	2	300
FY 1956	24,000	2	1	3	2	½	2½	300

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis Of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD - 62113-105
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Office of Director
LABORATORY

3.
SECTION

4.
LOCATION

5. NIAMD-67111-106
SERIAL NUMBER

6. Administration
PROJECT TITLE

7. Dr. Floyd S. Daft; Mr. W. G. Baylis
PRINCIPAL INVESTIGATORS

8. Mr. G. A. Brandner
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The major responsibility of the Office of the Director is to provide the overall executive direction and coordination of the laboratory, clinical and grants programs in order to achieve the objectives of the Institute, namely the conducting and supporting of research investigations concerned with the cause, diagnosis, treatment and prevention of arthritis, rheumatism and metabolic diseases. This immediate program direction is supplemented further by maintaining close relationships with national medical and scientific, as well as lay groups and non-Federal institutions, such as The Arthritis and Rheumatism Association, The Arthritis and Rheumatism Foundation, and, The American Diabetes Association, which are interested in dealing with the medical and economic problems posed by these disorders.

The Office of the Director includes a small staff which assists in furnishing the executive direction and administrative management services to the laboratory, clinical and extramural program areas of the Institute.

Significant Contributions: During the past year the National Institute of Arthritis and Metabolic Diseases was host to several meetings and conferences held at the Clinical Center by private medical, scientific and lay organizations. These included, the National Conference on Research and Education in the Rheumatic Diseases, sponsored by the American Rheumatism Association, the Arthritis and Rheumatism Foundation and the National Institute of

9. PROJECT DESCRIPTION - Continued

Arthritis and Metabolic Diseases; the First Interim Scientific Session of the American Rheumatism Association, and the Annual Meeting of the D. C. Chapter of the Arthritis and Rheumatism Foundation. The staff of the Director's Office handled all of the preliminary arrangements regarding space, invitations, hotel reservations, printing of programs, tours of the Clinical Center and exhibits in the Laboratory and Clinical Areas of NIAMD in the Clinical Center.

In the past year the position of Associate Director in Charge of Research was created and filled through the employment of Dr. DeWitt Stetten Jr., an outstanding authority in the field of Intermediary metabolism. By the end of the year the integration of this position into the Institute's framework has been accomplished and a most satisfactory management pattern has evolved and has proven most effective in providing thenecessary coordination of the Laboratory Research and Clinical Investigations areas of activity.

Another project which involved considerable effort was the preparation of plans for laboratory alterations in Buildings 2 and 4, as well as formulation of plans for the moves of the various organizational segments of the Institute that will be involved. Some of these renovations and moves have already been accomplished.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIAMD-67111-106
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$62,100	4	6	10	4	6	10	-
FY 1956	$62,100	4	6	10	4	6	10	-

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☒
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITH NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD-67111-106
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

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